Optimal control and cost-effectiveness analysis of an echinococcosis transmission model with interventions

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Abstract: A dynamical model of echinococcosis transmission with optimal control strategies is presented. The basic reproduction number of the model is obtained and used to study the stability of the disease-free and endemic equilibrium points. Sensitivity analysis of the basic reproduction number to the model parameters and control variables is performed. It finds that the natural death of dogs has a strong impact on the basic reproduction and the only anthelmintic treatment against echinococcosis does not eliminate the disease. The optimal control problem is formulated and solved analytically. Numerical simulations show that optimal control strategies could effectively eliminate the transmission of echinococcosis and the disinfection or cleaning of environment may shorten the time of eliminating the disease. The cost-effectiveness analysis suggests that a combination of health education and anthelmintic treatment could provide the best cost-effective strategy to control the transmission of echinococcosis. The findings could be helpful for the prevention and control of echinococcosis in Ganzi Tibetan Autonomous Prefecture, China and other areas of echinococcosis.

Keywords: Echinococcosis; basic reproduction number; global stability; sensitivity analysis; optimal control; cost-effectiveness.

1. Introduction

Echinococcosis, often referred to as hydatid disease, is a zoonotic parasitic disease, which is distributed in most areas of the world and imposes a heavy economic and health burden [1]. The life cycle of Echinococcus granulosus mainly relies on two different types of hosts: definitive and intermediate. Carnivores, such as dogs, act as definitive hosts while herbivores, such as sheep and cattle, are usually intermediate hosts. The definitive hosts are infected through the consumption of viscera of intermediate hosts that contain the parasite larvae. The parasite larvae develop into the mature tapeworm in the intestine of definitive hosts. The adult worms release eggs that are passed in the feces of definitive hosts. The intermediate hosts become infected by ingesting the parasite eggs in contaminated food and water. The parasite eggs then develop into larval stages in the viscera. Humans act as accidental intermediate hosts that acquire an infection in the same way as other intermediate hosts. However, humans are not involved in transmitting the infection to the definitive host since they do not biologically contribute to perpetuating the parasite's life cycle. For more knowledge about echinococcosis, please refer to [1–3].

In [4], a deterministic compartment model that described the transmission of echinococcosis among dogs, livestock, and human populations in Xinjiang was proposed to explore

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effective prevention and control measures. Their results showed that the basic reproduction number completely determined the dynamics of the model. A sensitivity analysis of the parameters from the basic reproduction number implied that the health education for people should be strengthened to reduce the transmission rate between livestock to dogs and the anthelmintic treatment for infected dogs should be increased through increasing the frequency of dog anthelmintic. Tang et al. [5] developed a discrete model from [4]. Based on the model of Wang et al. [4], Li and Teng [6] discussed a delayed stochastic echinococcosis epidemic model. In [7], the impact of dogs' migration among patches on the spread of echinococcosis was investigated by a patch model, which showed that the smaller diffusion of dogs was beneficial for disease control. Liu et al. [8] presented a time-delayed echinococcosis transmission model. In [9], an echinococcosis epidemic model with distributed delays was proposed. Xu and Ai [10] investigated the stability and traveling waves of a time-delayed and diffusive echinococcosis transmission model. Rong et al. [11] studied the special role of stray dogs and the potential effect of disposing stray dogs on the transmission of echinococcosis. They emphasized that without disposing of stray dogs, the disease became endemic even if the domestic dogs were controlled. Zhu et al. [12] explored the dynamics of echinococcosis transmission among multiple species and put forward that the interaction patterns among these species played a key role in echinococcosis transmission.

Wu et al. [13] studied the transmission dynamics of echinococcus with human intervention. In their model, the human interventions were considered as the implementation of deworming echinococcosis eggs and killing wild dogs. Hassan and Munganga [14] considered a new model for the transmission dynamics of echinococcus multilocularis that assessed the impact of environment disinfection or cleaning as control strategies on the disease dynamics. In their paper, the global sensitivity of parameters on the basic reproduction number of the model showed that the rates of cleaning or disinfecting the environment and rate of treating red foxes had the most global influence on the basic reproduction number. they further pointed out that the implementation of either of treatment on red foxes and the cleaning or disinfecting the environment should not be adequate in eradicating the parasite from the community and combining the two control strategies was more effective for controlling transmission of disease in the populations. Khan et al. [15] presented a discrete mathematical framework that describes the transmission dynamics and control measures of echinococcus multilocularis in foxes. They pointed out that this model should be an accurate and robust tool to analyze and control the parasite dynamics.

Although some mathematical models have included the prevention and control measures of echinococcosis(health education [11], anthelmintic treatment [4, 7–9, 11, 14, 16] and disinfection or cleaning of environment [13, 14]), there are few models that consider all the three control measures. Thus, a deterministic compartment model that includes all the three control measures will be studied. From [4, 11–13], human infection had no effect on the basic reproduction number. Humans will be not considered in the model framework, since humans are accidental intermediate hosts in echinococcosis transmission and they are not biologically contributing to transmitting the infection to the definitive host. In [13], they assumed that human efforts in deworming echinococcosis eggs and deeply buried dog feces should be proportional to the human population. However, the implementation of deworming echinococcosis eggs and deep buried dog feces is often planned regularly by the local government and there

are people hired to carry out such this plan. So, the death rate induced by the disinfection or cleaning of environment is assumed to be a constant in our model framework, which is consistent with Hassan and Munganga [14]. Of course, the mortality rate induced by the disinfection or cleaning of environment can be controlled by adjusting the frequency of the disinfection or cleaning of environment. Although Hassan and Munganga [14] had shown that the combined control effect was better than the single one, they did not consider how to make the integrated control better. Therefore, the optimal control of all the three control measures will be considered to explore the disease control strategy, which aims to reduce the number of infected individuals at a lower cost level (see [17–22] for example). furthermore, the cost-effectiveness analysis will be used to find the best cost-effective strategy (see [17,19,21,23–25] for example). Hence, to reduce and eliminate the spread of echinococcosis between dogs and livestock by comprehensive interventions with optimal control will be studied in the following.

In this paper, a mathematical model is proposed to study optimal control analysis of echinococcosis infection that includes comprehensive interventions (the use of health education, anthelmintic treatment, and disinfection or cleaning of environment). A dynamical model of echinococcosis transmission with controls is formulated in Section 2. Mathematical analysis of the model is presented in Section 3. The positivity and boundedness of solutions, equilibrium points, stability analysis, and sensitivity of the basic reproduction number to parameters and controls in the model are mainly considered. The optimal control problem is formulated in Section 4. Comparison of different control strategies and cost-effectiveness analysis are performed in Section 5. A brief conclusion and discussion are given in Section 6.

2. Model Formulation

The definitive host dog population is divided into susceptible $S_d(t)$ and infected $I_d(t)$. As intermediate hosts, the livestock population (mainly sheep and cattle) is decomposed into susceptible $S_l(t)$ and infected $I_l(t)$. The definitive host becomes infected by ingesting the cyst-containing organs of the infected intermediate host.The intermediate host is infected by ingesting echinococcosis eggs. The density of echinococcosis eggs that are released in the feces of infected dogs is denoted by $E(t)$. Since humans are aberrant intermediate hosts and do not involve in the transmission of echinococcosis, humans as the accident intermediate hosts are not considered in modeling framework. A schematic diagram for the dynamical transmission of echinococcus is illustrated in Fig.1. Based on this schematic diagram, it is established by the following transmission model:

$$\begin{cases} \dot{S}_d = \Lambda_d - (1-u_1(t))\beta_d S_d I_l - \mu_d S_d + \sigma u_2(t) I_d, \\ \dot{I}_d = (1-u_1(t))\beta_d S_d I_l - \mu_d I_d - \sigma u_2(t) I_d, \\ \dot{S}_l = \Lambda_l - \beta_l S_l E - \mu_l S_l, \\ \dot{I}_l = \beta_l S_l E - \mu_l I_l, \\ \dot{E} = \gamma I_d - \mu_e E - c_h u_3(t) E. \end{cases} \tag{1}$$

For the dog population, Λ_d is the annual recruitment rate of susceptible individuals, μ_d represents the natural death rate.σ denotes the recovery rate of infectious dogs due to anthelmintic treatment. $u_2(t) \in [0,1]$ is the control on the use of anthelmintic treatment.

$(1-u_1)\beta_d S_d I_l$ describes the transmission of echinococcosis between susceptible definitive hosts and infectious intermediate hosts, where $u_1(t) \in [0,1]$ is the control on the use of health education that refers to the imparting of echinococcosis knowledge. For the intermediate hosts, Λ_l represents the annual recruitment rate of susceptible individuals, μ_l is the natural death rate, $\beta_l S_l E$ depicts the transmission of echinococcosis eggs to intermediate hosts by ingesting the parasite eggs in the environment. For echinococcus eggs, γ is the released rate of infectious definitive hosts, c_h accounts for the losing rate of echinococcosis eggs because of disinfection or cleaning of environment. $u_3(t) \in [0,1]$ is the control on the use of disinfection or cleaning of environment. Echinococcosis eggs released by infected dogs could survive in the surroundings such as dog's fur, water, vegetables, soil, fomites and pastures (see [4, 12, 26]) for several weeks, and be assumed to die at a rate μ_e.

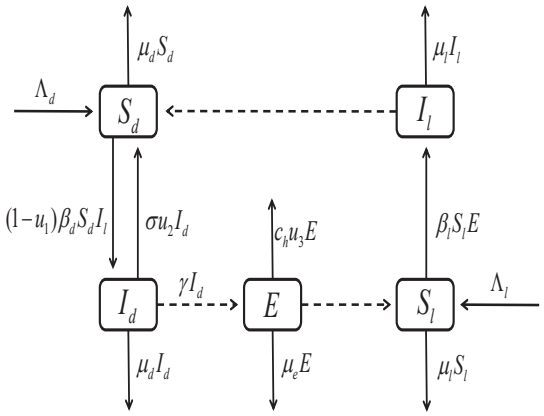

Fig. 1. Schematic diagram of the transmission dynamics of echinococcus.

3. Model Analysis

Some mathematical analysis results of model (1) can be obtained when all the control variables are supposed to be constant.

3.1. Positivity and boundary of solutions

Theorem 3.1 (i) The solution of model(1) with positive initial conditions remains positive for all $t > 0$.
(ii) All positive solutions of model (1) with positive initial conditions ultimately have the upper boundary in $\mathbb{R}^5_+$.

Proof. (i) Assume that $(S_d(t), I_d(t), S_l(t), I_l(t), E(t))$ is a solution of model (1) with positive initial values. Define

$$t_1 = \sup\left\{t > 0 : S_d(\tau) > 0, I_d(\tau) > 0, S_l(\tau) > 0, I_l(\tau) > 0, E(\tau) > 0\right\}$$

for all $\tau \in [0, t]$.

Since $\min\left\{S_d(0), I_d(0), S_l(0), I_l(0), E(0)\right\} > 0$, then there must be $t_1 > 0$. If $t_1 < \infty$, it gives

$$\min\left\{S_d(t_1), I_d(t_1), S_l(t_1), I_l(t_1), E(t_1)\right\} = 0,$$

and $S_d(t) > 0, I_d(t) > 0, S_l(t) > 0, I_l(t) > 0, E(t) > 0$ for all $t \in [0, t_1)$.

On the other hand, the first equation of model (1) is equivalent to

$$\frac{d}{dt}\left[S_d \exp\left(\int_0^t \left((1-u_1)\beta_d I_l + \mu_d\right) ds\right)\right] = \left(\Lambda_d + \sigma u_2 I_d\right) \exp\left(\int_0^t \left(\left(1-u_1\right)\beta_d I_l + \mu_d\right) ds\right).$$

Consequently,

$$\begin{aligned} S_d(t_1) =& S_d(0) \exp\left(-\int_0^{t_1} \left(\left(1-u_1\right)\beta_d I_l + \mu_d\right) dt\right) + \exp\left(-\int_0^{t_1} \left(\left(1-u_1\right)\beta_d I_l + \mu_d\right) dt\right) \\ & \times \int_0^{t_1} \left[\left(\Lambda_d + \sigma u_2 I_d\right) \left(\exp\left(\int_0^t \left(\left(1-u_1\right)\beta_d I_l + \mu_d\right) ds\right)\right)\right] dt, \end{aligned}$$

which implies that $S_d(t_1) > 0$. A similar approach could be applied to show that $I_d(t_1) > 0, S_l(t_1) > 0, I_l(t_1) > 0$ and $E(t_1) > 0$, which is a contradiction. So, $t_1 = \infty$.

Hence, all solutions of model (1) with positive initial conditions remain positive when $t > 0$.

(ii) From the first two equations of model (1), it follows that

$$\frac{d\left(S_d + I_d\right)}{dt} = \Lambda_d - \mu_d\left(S_d + I_d\right) \leqslant \Lambda_d - \mu_d\left(S_d + I_d\right).$$

Then $\limsup_{t\to\infty}\left(S_d + I_d\right) \leqslant \frac{\Lambda_d}{\mu_d}$.

Therefore, from the last equation of model(1), there is

$$\frac{dE}{dt} = \gamma I_d - \left(\mu_e + c_h u_3\right) E \leqslant \frac{\gamma\Lambda_d}{\mu_d} - \left(\mu_e + c_h u_3\right) E.$$

It follows that $\limsup_{t\to\infty} E \leqslant \frac{\gamma\Lambda_d}{\mu_d(\mu_e + c_h u_3)} \leqslant \frac{\gamma\Lambda_d}{\mu_d\mu_e}$.

Considering the third and fourth equations of model (1), it gives

$$\frac{d\left(S_l + I_l\right)}{dt} = \Lambda_l - \mu_l\left(S_l + I_l\right) \leqslant \Lambda_l - \mu_l\left(S_l + I_l\right),$$

which results in $\limsup_{t\to\infty}\left(S_l + I_l\right) \leqslant \frac{\Lambda_l}{\mu_l}$.

Let

$$\Omega = \left\{(S_d, I_d, S_l, I_l, E) \in \mathbb{R}^5_+ : S_d + I_d \leqslant \frac{\Lambda_d}{\mu_d}, S_l + I_l \leqslant \frac{\Lambda_l}{\mu_l}, E \leqslant \frac{\gamma\Lambda_d}{\mu_d\mu_e}\right\}. \tag{2}$$

All positive solutions of model (1) with positive initial conditions ultimately turn into Ω. Thus, the closed set Ω is positively invariant and globally attractive for model (1). This

completes the proof.

3.2. Equilibrium points and stability analysis

The disease-free equilibrium of model (1) is denoted by

$$E_{dfe} = \left(S_d^0, 0, S_l^0, 0, 0\right) = \left(\frac{\Lambda_d}{\mu_d}, 0, \frac{\Lambda_l}{\mu_l}, 0, 0\right).$$

In the following steps, the concept of next-generation matrix approach [27] will be used to compute the basic reproduction number $\mathscr{R}_0$. Define the matrix of new infection $\mathcal{F}$ and the matrix of transition $\mathcal{V}$ as follows

$$\mathcal{F} = \begin{bmatrix} (1-u_1)\beta_d S_d I_l \\ \beta_l S_l E \\ \gamma I_d \end{bmatrix}, \quad \mathcal{V} = \begin{bmatrix} (\mu_d + \sigma u_2)\, I_d \\ \mu_l I_l \\ (\mu_e + c_h u_3)\, E \end{bmatrix}.$$

Then the Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$ at the disease-free equilibrium E_{dfe} are respectively given by

$$F = \begin{bmatrix} 0 & \frac{(1-u_1)\beta_d \Lambda_d}{\mu_d} & 0 \\ 0 & 0 & \frac{\beta_l \Lambda_l}{\mu_l} \\ \gamma & 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \mu_d + \sigma u_2 & 0 & 0 \\ 0 & \mu_l & 0 \\ 0 & 0 & \mu_e + c_h u_3 \end{bmatrix}.$$

Moreover, the spectral radius ρ of FV^{-1} is the largest eigenvalue with large domain of the next generation matrix. Therefore, the basic reproduction number of model (1) is obtained by

$$\mathscr{R}_0 = \rho\left(FV^{-1}\right) = \sqrt[3]{\mathscr{R}_{0d} \cdot \mathscr{R}_{0l} \cdot \mathscr{R}_{0e}}, \tag{3}$$

where

$$\mathscr{R}_{0e} = \frac{\gamma}{\mu_e + c_h u_3}, \quad \mathscr{R}_{0d} = \frac{1}{\mu_d + \sigma u_2} \cdot \frac{\Lambda_d}{\mu_d} \cdot (1-u_1)\,\beta_d, \quad \mathscr{R}_{0l} = \frac{1}{\mu_l} \cdot \frac{\Lambda_l}{\mu_l} \cdot \beta_l.$$

Here, $\mathscr{R}_{0e}$ indicates the average number of echinococcosis eggs that might be ingested by the intermediate host livestock. $\mathscr{R}_{0l}$ accounts for the average number of infected livestock by echinococcosis eggs. $\mathscr{R}_{0d}$ represents the average number of infected dogs by infectious livestock. The third root of (3) is a geometric mean that measures the average change rate of $\mathscr{R}_{0e}$,$\mathscr{R}_{0d}$ and $\mathscr{R}_{0l}$ (see [29]). For more ecological and epidemiological significance in (3), please refer to [4, 13, 27].

Suppose $E_{ee} = (S_d^*, I_d^*, S_l^*, I_l^*, E^*)$ should be the endemic equilibrium of model (1). Let all of the right-hand sides of model (1) be zero. Solving these equations, it follows that

$$\begin{aligned} S_d^* &= \frac{(\mu_d + \sigma u_2)\, I_d^*}{(1-u_1)\beta_d I_l^*}, \quad I_d^* = \frac{\mu_e + c_h u_3}{\gamma} E^*, \quad S_l^* = \frac{\Lambda_l}{\beta_l E^* + \mu_l}, \\ I_l^* &= \frac{\beta_l}{\mu_l} S_l^* E^*, \quad E^* = \frac{(\mu_d + \sigma u_2)\, \mu_l^2}{\beta_l \left[(\mu_d + \sigma u_2)\, \mu_l + (1-u_1)\beta_d \Lambda_l\right]} \left(\mathscr{R}_0^3 - 1\right). \end{aligned}$$

Hence, model (1) has a uniquely endemic equilibrium E_{ee} if and only if $\mathscr{R}_0 > 1$.

Using the method similar to [4, 11],the following results can be obtained. In Appendix A, the proof of Theorem 3.2 is in detail presented. Appendix B gives the specific proof of Theorem 3.3. The concrete proof of Theorem 3.4 can be displayed in Appendix C.

Theorem 3.2 The disease-free equilibrium E_{dfe} is locally asymptotically stable if $\mathscr{R}_0 < 1$ and is unstable if $\mathscr{R}_0 > 1$.

Theorem 3.3 The disease-free equilibrium E_{dfe} is globally asymptotically stable if $\mathscr{R}_0 < 1$.

Theorem 3.4 The uniquely endemic equilibrium E_{ee} of model(1) is globally asymptotically stable if $\mathscr{R}_0 > 1$.

Table 1
Description of parameters of of model (1).

Parameters	Interpretation	Units	Source
Λ_d	Recruitment rate of dogs	21.1×10^4 year^{-1}	Estimated
β_d	Transmission rate from livestock to dogs	5.8×10^{-8} year^{-1}	[4]
μ_d	Natural death rate of dogs	0.08 year^{-1}	[4]
σ	Recovery rate of infected dogs with anthelmintic treatment	0.21 year^{-1}	Estimated
Λ_l	Recruitment rate of livestock	54.33×10^4 year^{-1}	Estimated
β_l	Transmission rate from echinococcosis eggs to livestock	7.4×10^{-8}year^{-1}	[4]
μ_l	Natural death rate of livestock	0.152 year^{-1}	[11]
γ	Released rate from infected dogs	9.7 year^{-1}	[4]
μ_e	Parasite egg mortality rate	1 year^{-1}	[13]
c_h	Disinfection or cleaning of environment induced parasite egg mortality rate	10 year^{-1}	Assumed
$u_1(t)$	Effectiveness of health education	$0-1$	Assumed
$u_2(t)$	Effectiveness of anthelmintic treatment	$0-1$	Assumed
$u_3(t)$	Effectiveness of disinfection or cleaning of environment	$0-1$	Assumed

3.3. Sensitivity of basic reproduction numbers to parameters and controls

Sensitivity analysis of the basic reproduction number to parameters and control variables is needed to estimate the parameters of model (1). Some of the parameter values in model (1) are adopted from references (see Table 1). Λ_d and Λ_l are estimated by using the data from Ganzi Tibetan Autonomous Prefecture, Sichuan Province of China, which are respectively

based on Statistics Bureau of Ganzi Tibetan Autonomous Prefecture [32] and Zou [33]. σ is computed according to [33]. The death rate of echinococcus eggs due to the behavior of disinfection or cleaning of environment cannot be directly measured. The parasite egg mortality rate induced by disinfection or cleaning of environment is assumed to reach ten times that of the natural death rate. Λ_d, β_d, μ_d,Λ_l, β_l,μ_l, γ, and μ_e are regarded as random variables. Each of these random variables takes a normal distribution with the mean value listed in Table 1 and standard deviation that is assumed to be one-tenth of its mean value. With 2000 runs of Latin hypercube sampling, the frequency distribution of $\mathscr{R}_0$ without controls is shown in Fig.2 (a). It displays that echinococcosis is statistically prevalent when there is no prevention and control for this disease. The partial rank correlation coefficients (PRCCs) [34] are computed to analyze the sensitivity of $\mathscr{R}_0$ without control measures since the model parameters may exhibit some uncertainty in determining or selecting experimental data. Fig.2 (b) displays the bar chart of PRCCs. The PRCC value close to $+1$ or -1 means that there exists a strong correlation between the input parameters and the outcome measures. The natural death rate of dogs shown in Fig.2 (b) has the greatest influence on the basic reproduction number. It agrees with that removal or reduction in worm biomass in definitive hosts (usually dogs) will have the greatest and quickest effect to reduce active transmission [35]. It should be emphasized that the parameters with large PRCC values (> 0.5 or < -0.5) as well as corresponding small p-values are the most important [34]. Fig.2(b) shows that each of the parameters Λ_d, β_d, μ_d,Λ_l, β_l,μ_l, γ, and μ_e is very important for the basic reproduction number $\mathscr{R}_0$ without control measures.

To assess the impact of control measures on the basic reproduction number $\mathscr{R}_0$, numerical experiments are implemented by varying the effectiveness of health education (u_1), anthelmintic treatment(u_2) and disinfection or cleaning of environment (u_3) ranging from 0 to 1. Fig.3 shows that the basic reproduction number $\mathscr{R}_0$ is considered as a function of u_1, u_2, u_3, respectively. With the use of control measures strengthened, $\mathscr{R}_0$ tends to get smaller. It is worth noting that $\mathscr{R}_0$ is the most sensitive to u_1 than u_2 and u_3, which could decrease to below the critical threshold unity along with u_1 increasing. Conversely, as u_2 increases, $\mathscr{R}_0$ cannot decrease to below the critical threshold. When u_3 increases, $\mathscr{R}_0$ cannot attain its critical value. This suggests that health education should be a very effective preventive against transmission of echinococcosis. Meanwhile, disinfection or cleaning of environment has the greatest impact on $\mathscr{R}_0$ when u_1, u_2, and u_3 change on the left side of point B. By contrast, health education has the slowest control effectiveness when u_1, u_2 and u_3 vary on the left side of point A. It motivates me to find the optimal solutions for all the controls.

4. Optimal control

To achieve the optimal control strategy, an objective functional is defined as follows:

$$J(u_1, u_2, u_3) = \int_0^{t_f} \left[I_d + I_l + E + \frac{1}{2}\left(k_1 u_1^2 + k_2 u_2^2 + k_3 u_3^2\right) \right] dt, \tag{4}$$

subject to the state system (1). k_1, k_2 and k_3 represent the weight constants on the benefit and cost. $\frac{k_1 u_1^2}{2}$, $\frac{k_2 u_2^2}{2}$, and $\frac{k_3 u_3^2}{2}$ denote costs of health education, anthelmintic treatment and

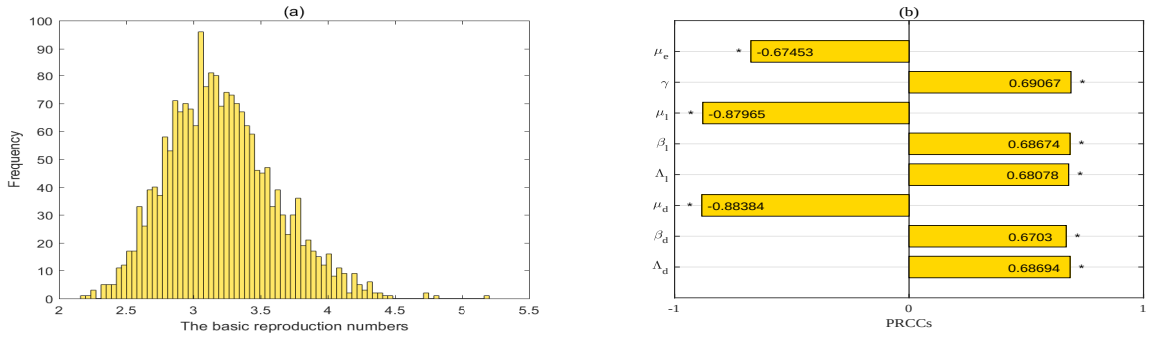

Fig. 2. (a) Frequency distribution of the basic reproduction number $\mathscr{R}_0$ without control measures. (b) Partial rank correlation coefficients of the basic reproduction number $\mathscr{R}_0$ without control measures. Parameters with a PRCC significantly $p < 0.005$ are indicated with (*).

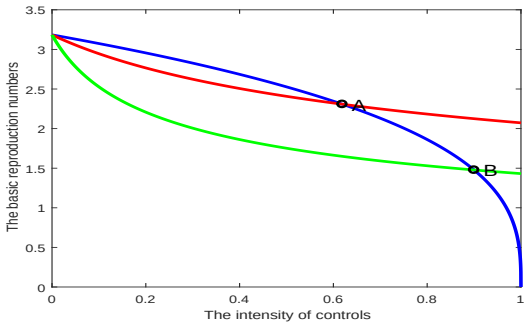

Fig. 3. Influence of control measures on the basic reproduction number $\mathscr{R}_0$. The blue curve represents $\mathscr{R}_0$ as a function of u_1 while $u_2 = 0$ and $u_3 = 0$. The red curve represents $\mathscr{R}_0$ as a function of u_2 while $u_1 = 0$ and $u_3 = 0$. The green curve represents $\mathscr{R}_0$ as a function of u_3 while $u_2 = 0$ and $u_2 = 0$. $A(0.6191, 2.3097)$ is the intersection of the blue and red lines. $B(0.9000, 1.4779)$ is the intersection of the blue and green lines.

disinfection or cleaning of environment,respectively.

The goal of optimal control is to determine a control set that minimizes the infected dogs, the infected livestock and parasite eggs when minimizing the control costs. Assume that $U = \{(u_1, u_2, u_3) : 0 \leqslant u_i(t) \leqslant 1, t \in [0, t_f], i = 1, 2, 3\}$ is a measurable control set. Then there is a need to find the optimal controls u_1^*, u_2^* and u_3^* satisfying

$$J(u_1^*, u_2^*, u_3^*) = \min \{J(u_1, u_2, u_3) : (u_1, u_2, u_3) \in U\}. \tag{5}$$

Pontryagin's Maximum Principle [36] is used to deduce the necessary conditions that determine the optimal controls u_1^*, u_2^* and u_3^* satisfying condition (5) with constraint model (1). This principle transforms the optimal control problem into minimizing the Hamiltonian function that represents

$$H = I_d + I_l + E + \frac{1}{2}\left(k_1 u_1^2 + k_2 u_2^2 + k_3 u_3^2\right) + \sum_{i=1}^{5} \lambda_i f_i, \tag{6}$$

with $f_i, i = 1, 2, 3, 4, 5$ denoting the right-hand sides of model (1). $\lambda_i, i = 1, 2, 3, 4, 5$ are the adjoint variables that satisfy the following co-state system:

$$\begin{cases} \dot{\lambda}_1 = -\frac{\partial H}{\partial S_d} = \lambda_1\left[(1-u_1)\beta_d I_l + \mu_d\right] - \lambda_2(1-u_1)\beta_d I_l, \\ \dot{\lambda}_2 = -\frac{\partial H}{\partial I_d} = -1 - \lambda_1\sigma u_2 + \lambda_2(\mu_d + \sigma u_2) - \lambda_5\gamma, \\ \dot{\lambda}_3 = -\frac{\partial H}{\partial S_l} = \lambda_3(\beta_l E + \mu_l) - \lambda_4\beta_l E, \\ \dot{\lambda}_4 = -\frac{\partial H}{\partial I_l} = -1 + \lambda_1(1-u_1)\beta_d S_d - \lambda_2(1-u_1)\beta_d S_d + \lambda_4\mu_l, \\ \dot{\lambda}_5 = -\frac{\partial H}{\partial E} = -1 + \lambda_3\beta_l S_l - \lambda_4\beta_l S_l + \lambda_5(\mu_e + c_h u_3), \end{cases} \tag{7}$$

with boundary conditions $\lambda_i(t_f) = 0, i = 1, 2, 3, 4, 5$. Additionally, the optimality conditions $\frac{\partial H}{\partial u_i} = 0, i = 1, 2, 3$ yield the optimal controls:

$$u_i^* = \min\{1, \max\{0, u_i^c\}\}, i = 1, 2, 3, \tag{8}$$

where

$$u_1^c = \frac{\beta_d S_d I_l(\lambda_2 - \lambda_1)}{k_1}, u_2^c = \frac{\sigma I_d(\lambda_2 - \lambda_1)}{k_2}, u_3^c = \frac{\lambda_5 c_h E}{k_3}. \tag{9}$$

5. Comparison of different control strategies and cost-effectiveness analysis

5.1. Comparison of different control strategies

To study the effectiveness of optimal control, numerical simulations of different optimal controls scenarios are presented. The forward-backward sweep method [36] is used to find the numerical solutions of the optimality system. The state system (1) is solved numerically by Matlab (ode45 solver). The initial condition is assumed to be taken as $S_d(0) = 1.686 \times 10^5$, $I_d(0) = 4 \times 10^4$, $S_l(0) = 3.335 \times 10^6$, $I_l(0) = 5 \times 10^5$, and $E(0) = 2 \times 10^7$, where $S_d(0)$ can be estimated from [32] and $S_l(0)$ can be estimated from [33]. The other initial values of model (1) are assumed. The backward Runge-Kutta scheme is implemented to solve the co-state

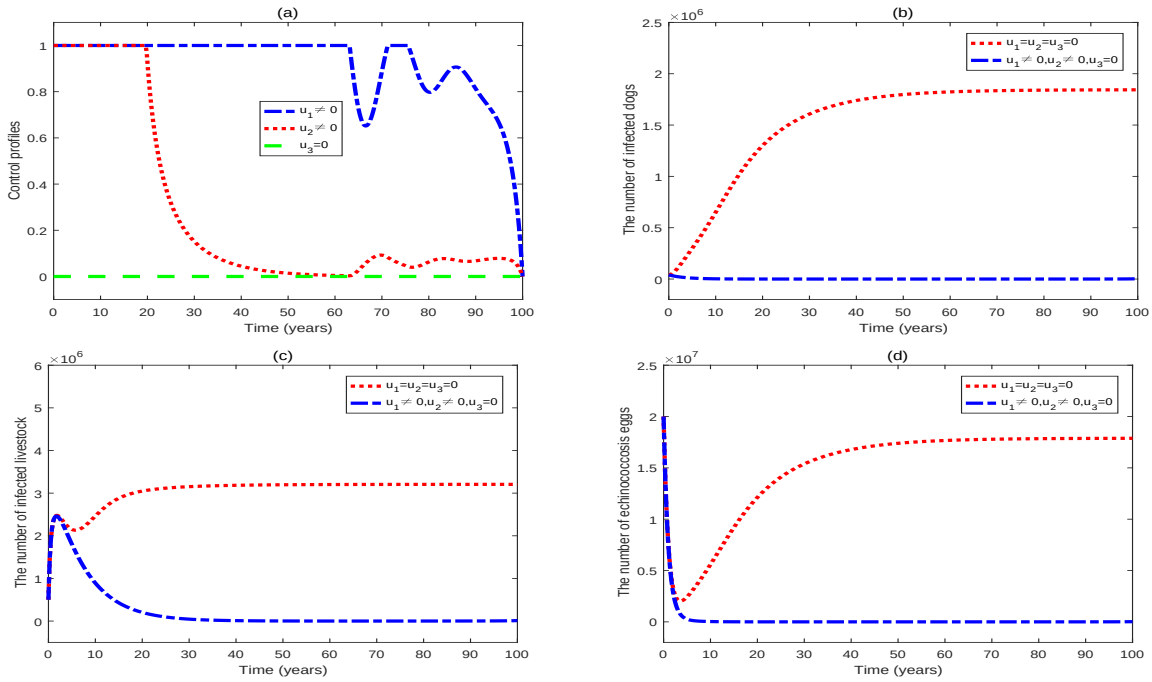

Fig. 4. Simulations depicting the effect of health education and anthelmintic treatment only on the transmission of echinococcosis.

system (7) with boundary conditions. The control variables (8) are updated by substituting the state and adjoint values until the current state, the adjoint and the control values are sufficiently close. It is the fact that the cost of anthelmintic treatment is more expensive than disinfection or cleaning of environment, while the cost of health education is cheaper than disinfection or cleaning of environment. So, the weighting constants are taken as $k_1 = 50$, $k_2 = 90$ and $k_3 = 70$. All other parameters are listed in Table 1. In particular, the four control strategies: **Strategy A**(Health education and anthelmintic treatment), **Strategy B**(Health education and disinfection or cleaning of environment), **Strategy C**(anthelmintic treatment and disinfection or cleaning of environment), and **Strategy D**(Health education, anthelmintic treatment, and disinfection or cleaning of environment) will be considered in the following.

For Strategy A, the health education control u_1 and the anthelmintic treatment control u_2 are utilized to optimize the objective functional (6) while the disinfection or cleaning of environment control is not used, i.e.,$u_3 = 0$. Fig.4(a) displays the control profiles of u_1^* and u_2^*. The health education (blue dash-dot line in Fig.4(a)) should be executed 100% for almost 63 years and thereafter, the control effort oscillates till the 86th year and then finally decreases gradually to zero in 14 years. Meanwhile, the anthelmintic treatment (red dotted line inFig.4(a)) keeps a 100% use for 20 years and then declines to a lower level. Thereafter, the control effort u_2^* oscillates till the 95th year and finally decreases to zero in 5 years. Remarkably, the control effort u_1^* in the oscillation mode decreases (increases) while the control effort u_2^* almost increases (decreases). This is anticipated because when the control effort u_1^* is reduced, the control effort u_2^* should be increased, and vice versa. Fig.4(b-d) show that the

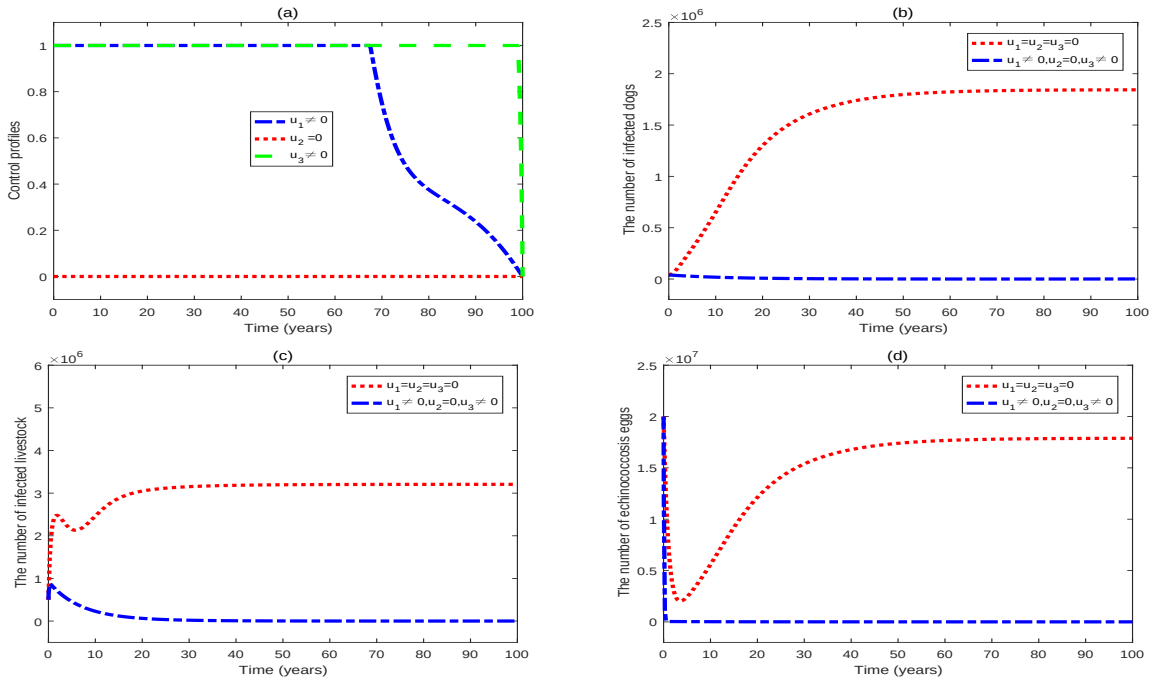

Fig. 5. Simulations depicting the effect of health education and disinfection or cleaning of environment only on transmission of echinococcosis.

number of infected dogs, infected livestock and echinococcosis eggs under Strategy A (blue dash-dot line) is significantly reduced to a lower level compared to the outputs of running model (1) without controls (red dotted line).

For Strategy B, the health education control u_1 and the disinfection or cleaning of environment control u_3 are utilized to optimize the objective function (6) while the anthelmintic treatment control u_2 is not used, i.e., $u_2 = 0$. Fig.5(a) displays the control profiles of u_1^* and u_3^*. The health education (blue dash-dot line in Fig.5(a)) should be done 100% intensively for almost 67 years and then the control effort is gradually decreased till the end of the intervention. Meanwhile, the disinfection or cleaning of environment control (green dashed line in Fig.5(a)) keeps a 100% use for almost 100 years and then declines to zero in the 100th year. It follows from Fig.5(b-d) that there is a significant difference among the number of infected dogs, infected livestock and echinococcosis eggs between the controlled cases (blue dash-dot line) and the cases without control (red dotted line).

For Strategy C, the anthelmintic treatment control u_2 and the disinfection or cleaning of environment control u_3 are utilized to optimize the objective function (6) while the health education control u_1 is not used, i.e., $u_1 = 0$. Fig.6(a) displays the control profiles of u_2^* and u_3^*. The anthelmintic treatment (red dotted line in Fig.6(a)) should be kept a 100% use for almost 96 years and then declines gradually till the end of this intervention. The control effort u_3^* needs to be kept a 100% use for almost 100 years and then declines to zero in the 100th year. It's based on the fact that the anthelmintic treatment control aims to reduce the number of infected dogs and then echinococcus eggs could be reduced. Fig.6(b-d) depict that

a combination of u_2^* and u_3^* has a significant difference for reducing the number of infected dogs, infected livestock and echinococcosis eggs (blue dash-dot line) than the cases without control (red dotted line).

For Strategy D, the health education control u_1, the anthelmintic treatment control u_2 and the disinfection or cleaning of environment control u_3 are implemented simultaneously to optimize the objective function (6). The optimal controls are displayed in Fig.7(a). The health education (blue dash-dot line in Fig.7(a)) should be done 100% intensively for almost 52 years and then declines gradually till the end of this intervention. While the anthelmintic treatment (red dotted line in Fig.7(a)) needs to be kept a 100% use for 17 years and then decrease to a lower level until the 52nd year. Thereafter, the control effort u_2^* increases from 1.03% in the 52nd year to 15.94% in the 68th year and then finally decreases gradually to zero in 32 years. Meanwhile, the disinfection or cleaning of environment control effort u_3^* (green dashed line in Fig.7(a)) should be done 100% intensively for almost 27 years and then declines to 25.22% in the 52nd year. Thereafter, the control effort u_3^* increases to an almost 100% use in the 60th year and keep 100% until the 97th year. After that u_3^* finally decreases gradually to zero until the end of this intervention. It can be observed in Fig.7(b-d) that Strategy D (blue dash-dot line) provides a significant reduction in infected dogs, infected livestock and echinococcosis eggs compared to the scenario without controls (red dotted line).

Table 2
Benefits and costs of different optimal control strategies.

Strategy	Total infection averted	Total cost	ICER relative to No control	ICER relative to next best strategy
No control	0	0	-	-
Strategy A	4.3626×10^8	6.3535×10^3	1.4564×10^{-5}	2.2961×10^{-4}
Strategy B	4.5234×10^8	1.0629×10^4	2.3637×10^{-5}	Dominated
Strategy C	4.4443×10^8	1.5798×10^4	3.5547×10^{-5}	Dominated
Strategy D	4.5323×10^8	1.0250×10^4	2.2614×10^{-5}	Dominated

5.2. Cost-effectiveness analysis

To identify the best cost-effective strategy, it needs to compare all control strategies. Cost-effectiveness analysis can quantify and compare the benefits and the costs with different control measures. Consequently, the most appropriate strategy can be further determined to be implemented according to the cost-effectiveness analysis. The incremental cost-effectiveness ratio (ICER) stated by Buonomo and Marca [17, 24] is used to perform the cost-effectiveness analysis for different control measures. $\int_0^{t_f} \sum_{i=1}^{3} k_i u_i^2 dt$ is supposed to represent the total cost. The total infection averted is considered as $\int_0^{t_f} \left[(I_d - I_d^*) + (I_l - I_l^*)\right] dt$, where I_d^* and I_l^* denote the optimal solutions associated with the corresponding strategy.

If there is no control, both the total infection averted and the cost will be equal to be zero. The cost-effectiveness of strategy A and B will be first compared. Then the ICERs are

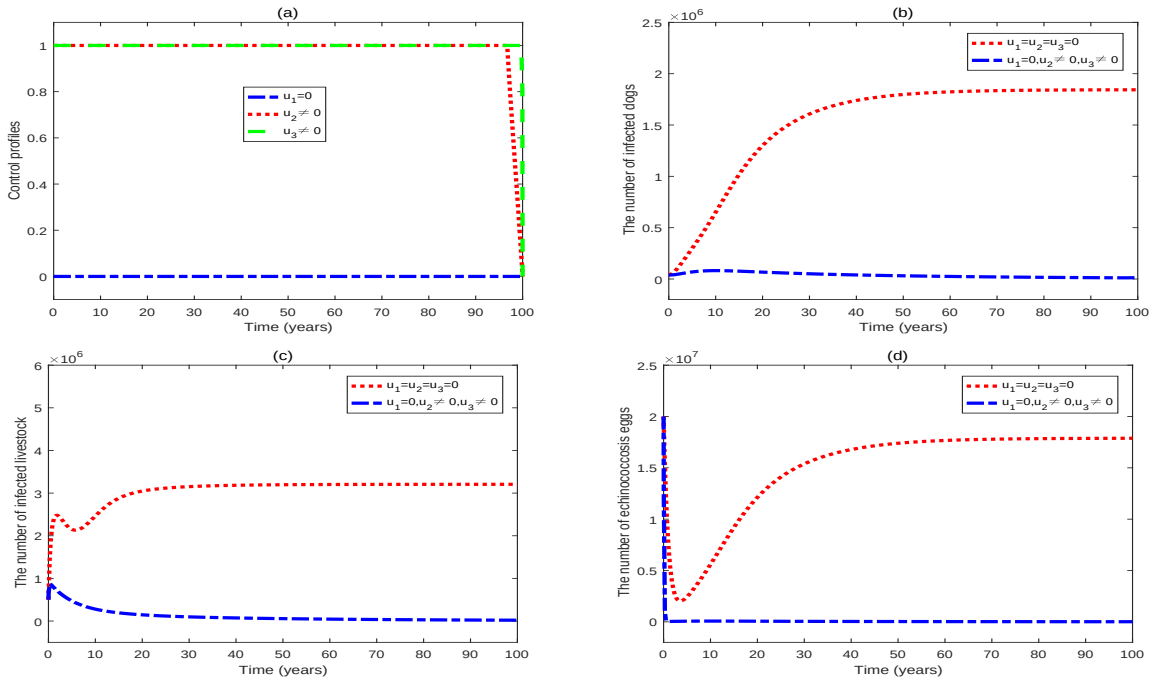

Fig. 6. Simulations depicting the effect of anthelmintic treatment and disinfection or cleaning of environment only on transmission of echinococcosis.

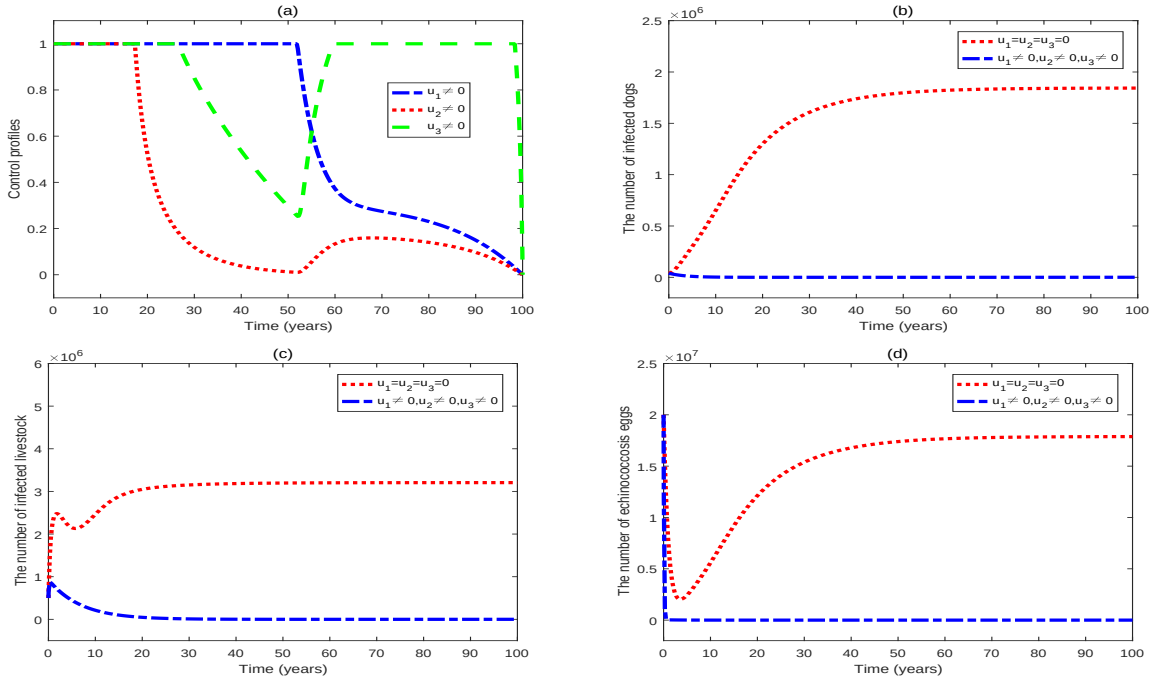

Fig. 7. Simulations depicting the effect of health education, anthelmintic treatment and disinfection or cleaning of environment on transmission of echinococcosis.

computed by

$$\text{ICER(A)} = \frac{6.3535 \times 10^3}{4.3626 \times 10^8} \approx 1.4564 \times 10^{-5},$$
$$\text{ICER(B)} = \frac{1.0629 \times 10^4 - 6.3535 \times 10^3}{4.5234 \times 10^8 - 4.3626 \times 10^8} \approx 2.6589 \times 10^{-4}.$$

From ICER(A) and ICER(B), Strategy A saves 2.6589×10^{-4} than Strategy B. So, Strategy B is dominated by Strategy A, i.e., Strategy B is more costly and less effective than Strategy A. Similarly, it could be computed from Table 2 that Strategy C is dominated by Strategy A and Strategy D is dominated by Strategy A. As is clear, Strategy A (a combination of health education and anthelmintic treatment) is deduced to be the best cost-effective of all the control strategies. It can be shown in a similar way that Strategy D is the next best cost-effective strategy, followed by Strategy C. Strategy B is the least cost-effective strategy.

6. Conclusion and disccusion

In this paper, an echinococcosis transmission model with the intervention of health education, anthelmintic treatment, and disinfection or cleaning of environment is formulated and analyzed. The basic reproduction number $\mathscr{R}_0$ is obtained by using the next-generation matrix method [27]. When $\mathscr{R}_0 < 1$, the disease-free equilibrium is globally asymptotically stable, i.e., this disease will be extinction. Conversely, when $\mathscr{R}_0 > 1$, the disease-free equilibrium is unstable and the endemic equilibrium is globally asymptotically stable, i.e., this disease will persist at that point and be endemic. Fig.2(a) shows that if there is no prevention and control for echinococcosis transmission, this disease will be endemic in Ganzi Tibetan Autonomous Prefecture. Although in the western China Echinococcosis Control Programme is working by the dog-dosing frequency monthly, however, this is very difficult to achieve especially in scattered semi-nomadic remote communities [35]. If the monthly deworming for all dogs in the control of echinococcus infection is only carried out, it can be observed from Fig.3 that in this case this disease is still prevalent. The anthelmintic treatment against echinococcosis does not eliminate the infection and most of the time when the treatments cease there is a rebound in the infection (see [35] for example). Thus, it is difficult to eliminate echinococcosis by only using the anthelmintic treatment. Instead, the comprehensive interventions (health education, anthelmintic treatment, and disinfection or cleaning of environment) are put into effect.

To effectively control the spread of echinococcosis, an optimal control problem is formulated and solved. Figs.4-7 display that each of Strategies A, B, C and D could reduce the number of infected dogs, infected livestock and echinococcus eggs to a low level. By considering the decline rate of infected livestock and echinococcosis eggs in Figs.4-7, Strategy A takes the longest time to reduce the number of infected dogs, infected livestock and echinococcus eggs to a low level. Therefore, u_3 (disinfection or cleaning of environment) may be critical for the time of eliminating the disease. The cost-effectiveness analysis has shown that Strategy A is the best cost-effective of all the control strategies. However, to eradicate echinococcosis, the total number of averted infections may be more convincing than ICERs. It could be

observed from Table 2 that Strategy D has the most total infection averted among all control strategies and Strategy A has by contrary the least total infection averted. If the budget is sufficient, Strategy D will be the best choice.

This work highlights the following facts: (a) The only anthelmintic treatment against echinococcosis does not eliminate the infection; (b) The disinfection or cleaning of environment may reduce the time of eliminating the disease; (c) The control policy implementing either of the scenarios presented in this paper could eliminate this disease. Nevertheless, the system studied has some limitations. The life cycle of the parasite is not fully considered. Roberts et al. [37–40] pointed out that the life cycle of the parasite would be important for the model framework of echinococcosis transmission. In [35], they emphasized that the home slaughter inspection should be a key control measure to reduce the transmission of echinococcosis between dogs and livestock. Besides, although humans are dead-end hosts of an animal-centered parasite life cycle, human behaviors seriously affect the spread of echinococcosis. In the future work, the roles of the life cycle of the parasite, home slaughter inspection and human behaviors on the echinococcosis transmission dynamics will be discussed. Since Shiqu County in Ganzi Tibetan Autonomous Prefecture has an extremely high prevalence, the findings are expected to be helpful for prevention and control of echinococcosis and significantly reduce the infection rate of echinococcosis in Shiqu County.

Acknowledgment

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Appendix A. Proof of Theorem 3.2

The Jacobian matrix of model (1) evaluated at the disease-free equilibrium E_{dfe} is given by

$$J_0 = \begin{pmatrix} -\mu_d & \sigma u_2 & 0 & -\frac{(1-u_1)\beta_d \Lambda_d}{\mu_d} & 0 \\ 0 & -(\mu_d + \sigma u_2) & 0 & \frac{(1-u_1)\beta_d \Lambda_d}{\mu_d} & 0 \\ 0 & 0 & -\mu_l & 0 & -\frac{\beta_l \Lambda_l}{\mu_l} \\ 0 & 0 & 0 & -\mu_l & \frac{\beta_l \Lambda_l}{\mu_l} \\ 0 & \gamma & 0 & 0 & -(\mu_e + c_h u_3) \end{pmatrix}.$$

Then the characteristic polynomial of J_0 is

$$P(\lambda) = (\lambda + \mu_d)(\lambda + \mu_l)\left(\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0\right),$$

where

$$\begin{aligned} a_0 =& \mu_l(\mu_d + \sigma u_2)(\mu_e + c_h u_3)\left(1 - \mathscr{R}_0^3\right), \\ a_1 =& \mu_l(\mu_d + \sigma u_2) + (\mu_d + \sigma u_2)(\mu_e + c_h u_3) + \mu_l(\mu_e + c_h u_3), \\ a_2 =& \mu_l + (\mu_d + \sigma u_2) + (\mu_e + c_h u_3). \end{aligned} \tag{A.1}$$

Let $Q(\lambda) = \lambda^3 + a_2\lambda^2 + a_1\lambda + a_0$. It is evident from (A.1)that there are $a_1 > 0$ and $a_2 > 0$. If $\mathscr{R}_0 < 1$, then $a_0 > 0$. Furthermore,

$$a_1a_2 - a_0 = [\mu_l + (\mu_d + \sigma u_2)]\left[a_1 + (\mu_e + c_h u_3)^2\right] + \mu_l(\mu_d + \sigma u_2)(\mu_e + c_h u_3)\mathscr{R}_0^3 > 0.$$

Using Routh–Hurwitz conditions [28], all roots of $Q(\lambda)$ have negative real parts. Then it is clear that all roots of $P(\lambda)$ are also negative real parts0. Therefore, the disease-free equilibrium E_{dfe} is locally asymptotically stable when $\mathscr{R}_0 < 1$. By contrary, $Q(0) = a_0 < 0$ if $\mathscr{R}_0 > 1$. Since $\lim\limits_{\lambda\to+\infty} Q(\lambda) = +\infty$, there must be a positive root of $Q(\lambda)$ from the Intermediate Value Theorem. So, E_{dfe} is unstable if $\mathscr{R}_0 > 1$.

Appendix B. Proof of Theorem 3.3

Assume that $(S_d(t), I_d(t), S_l(t), I_l(t), E(t))$ is a solution of model (1) in Ω. Then it implies that $I_d(t) \leqslant \frac{\Lambda_d}{\mu_d}, I_l(t) \leqslant \frac{\Lambda_l}{\mu_l}$ for all $t \geqslant 0$. Consider a Lyapunov function defined by

$$\mathcal{L}(I_d, I_l, E) = I_d + \frac{(1-u_1)\beta_d\Lambda_d}{\mu_d\mu_l} I_l + \frac{\mu_d + \sigma u_2}{\gamma} E.$$

By computing the derivative of $\mathcal{L}$ along with the solutions of model (1), it leads to

$$\begin{aligned}
\frac{d\mathcal{L}}{dt} =& \dot{I}_d + \frac{(1-u_1)\beta_d\Lambda_d}{\mu_d\mu_l}\dot{I}_l + \frac{\mu_d + \sigma u_2}{\gamma}\dot{E} \\
=& \left((1-u_1)\beta_d S_d - \frac{(1-u_1)\beta_d\Lambda_d}{\mu_d}\right) I_l \\
&+ \left(\frac{(1-u_1)\beta_d\beta_l\Lambda_d}{\mu_d\mu_l} S_l - \frac{\mu_d + \sigma u_2}{\gamma}(\mu_e + c_h u_3)\right) E \\
\leqslant& \left(\frac{(1-u_1)\beta_d\beta_l\Lambda_d}{\mu_d\mu_l}\frac{\Lambda_l}{\mu_l} - \frac{\mu_d + \sigma u_2}{\gamma}(\mu_e + c_h u_3)\right) E \\
=& \frac{\mu_d + \sigma u_2}{\gamma}(\mu_e + c_h u_3)\left(\mathscr{R}_0^3 - 1\right) E.
\end{aligned}$$

So that $\dot{\mathcal{L}} < 0$ if $\mathscr{R}_0 < 1, E > 0$. Furthermore, $\dot{\mathcal{L}} = 0$ when $\mathscr{R}_0 < 1$, and $E = 0$. As a consequence, the only invariant set satisfying $\dot{\mathcal{L}} = 0$ is the singleton E_{dfe} when $\mathscr{R}_0 < 1$. By Lasalle's invariance principle [30], the disease-free equilibrium E_{dfe} is globally asymptotically stable if $\mathscr{R}_0 < 1$.

Appendix C. Proof of Theorem 3.4

Since $\dot{S}_d + \dot{I}_d = \Lambda_d - \mu_d(S_d + I_d)$, $\dot{S}_l + \dot{I}_l = \Lambda_l - \mu_l(S_l + I_l)$, it suggests that $\lim\limits_{t\to\infty}(S_d + I_d) = \frac{\Lambda_d}{\mu_d}$, $\lim\limits_{t\to\infty}(S_l + I_l) = \frac{\Lambda_l}{\mu_l}$. So that the long-term dynamical behaviors of $S_d(t)$ and $S_l(t)$ can be represented by $\frac{\Lambda_d}{\mu_d} - I_d(t)$ and $\frac{\Lambda_l}{\mu_l} - I_l(t)$, respectively. Consider the subsystem of model (1)

as follows:

$$\begin{cases} \dot{I}_d = (1-u_1)\beta_d S_d I_l - \mu_d I_d - \sigma u_2 I_d, \\ \dot{I}_l = \beta_l S_l E - \mu_l I_l, \\ \dot{E} = \gamma I_d - \mu_e E - c_h u_3 E. \end{cases} \tag{C.1}$$

Let

$$\Delta = \left\{ (I_d, I_l, E) \in \mathbb{R}^3_+ : I_d \leqslant \frac{\Lambda_d}{\mu_d}, I_l \leqslant \frac{\Lambda_l}{\mu_l}, E \leqslant \frac{\gamma \Lambda_d}{\mu_d \mu_e} \right\}.$$

The dynamics of model (C.1) could be focused on this region Δ because Ω is positively invariant for model (1). To study the global stability of model (C.1) at (I_d^*, I_l^*, E^*), the method in [31] is adopted. Define

$$h(\boldsymbol{v}) = \begin{pmatrix} h_1(v_1, v_2, v_3) \\ h_2(v_1, v_2, v_3) \\ h_3(v_1, v_2, v_3) \end{pmatrix} = \begin{pmatrix} -(\mu_d + \sigma u_2) v_1 + (1-u_1)\beta_d \left(\frac{\Lambda_d}{\mu_d} - v_1 \right) v_2 \\ -\mu_l v_2 + \beta_l \left(\frac{\Lambda_l}{\mu_l} - v_2 \right) v_3 \\ -(\mu_e + c_h u_3) v_3 + \gamma v_1 \end{pmatrix}.$$

Then $h : \mathbb{R}^3_+ \mapsto \mathbb{R}^3_+$ is a continuously differential map. It thus leads to $h(\mathbf{0}) = \mathbf{0}$,and $h_i(\boldsymbol{v}) \geqslant 0, i = 1, 2, 3$ for all $\boldsymbol{v} \in \Delta$ when $v_i = 0$. Furthermore, there is $\frac{\partial h_i}{\partial v_j} \geqslant 0, i \neq j$ for $\boldsymbol{v} \in \Delta$. So, h is cooperative on Δ.

For $p \in (0, 1)$ and $\boldsymbol{v} \in \Delta$, it follows that

$$\begin{aligned} h_1(pv_1, pv_2, pv_3) =& -(\mu_d + \sigma u_2) pv_1 + (1-u_1)\beta_d \left(\frac{\Lambda_d}{\mu_d} - pv_1 \right) pv_2 \\ \geqslant& -(\mu_d + \sigma u_2) pv_1 + (1-u_1)\beta_d \left(\frac{\Lambda_d}{\mu_d} - v_1 \right) pv_2 \\ =& p h_1(v_1, v_2, v_3). \end{aligned}$$

Similarly, it is found that $h_i(pv_1, pv_2, pv_3) \geqslant p h_i(v_1, v_2, v_3), i = 2, 3$. Hence, h is strictly sublinear on Δ.

By calculating $Dh(\boldsymbol{v}) = \left(\frac{\partial h_i}{\partial v_j} \right) \big|_{1 \leq i,j \leqslant 3}$, it gives rise to

$$Dh(\boldsymbol{v}) = \begin{pmatrix} -(\mu_d + \sigma u_2) - (1-u_1)\beta_d v_2 & (1-u_1)\beta_d \left(\frac{\Lambda_d}{\mu_d} - v_1 \right) & 0 \\ 0 & -\mu_l - \beta_l v_3 & \beta_l \left(\frac{\Lambda_l}{\mu_l} - v_2 \right) \\ \gamma & 0 & -(\mu_e + c_h u_3) \end{pmatrix}.$$

Then $Dh(\boldsymbol{v})$ is irreducible on $\boldsymbol{v} \in \Delta$ because $|Dh(\boldsymbol{v})| \neq 0$. A straightforward computation shows that

$$Dh(\mathbf{0}) = \begin{pmatrix} -(\mu_d + \sigma u_2) & (1-u_1)\beta_d \frac{\Lambda_d}{\mu_d} & 0 \\ 0 & -\mu_l & \beta_l \frac{\Lambda_l}{\mu_l} \\ \gamma & 0 & -(\mu_e + c_h u_3) \end{pmatrix}.$$

Therefore, the characteristic polynomial of $Dh(\mathbf{0})$ is

$$Q(\lambda) = \lambda^3 + a_2 \lambda^2 + a_1 \lambda + a_0,$$

where a_0, a_1 and a_2 are known from (A.1). Then $a_0 < 0$ when $\mathscr{R}_0 > 1$. According to the proof process of Theorem 3.3, there must exist a positive root of $Q(\lambda)$. So, $s(Dh(\mathbf{0})) = \max\{\mathrm{Re}\lambda : Q(\lambda)\} > 0$.

From Corollary 3.2 in [31], it could be concluded that the positive equilibrium point (I_d^*, I_l^*, E^*) of model (C.1) is globally asymptotically stable. Hence, it is further obtained that the endemic equilibrium E_{ee} of model (1) is globally asymptotically stable.

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