Modeling the Transmission Dynamics of Rabies for Dog, Chinese Ferret Badger and Human Interactions in Zhejiang Province, China*

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Abstract

Human rabies is one of the major public-health problems in China with an average of 1977 cases per year. It is estimated that 95% of these human rabies cases are due to dog bites. In recent years, the number of wildlife-associated human rabies cases has increased, particularly in the southeast and northeast regions of mainland China. Chinese ferret badgers (CFB) are one of the most popular wildlife animals which are distributed mostly in the southeast region of China. Human cases caused by rabid CFB were first recorded in Huzhou, Zhejiang Province, in 1994. From 1996 to 2004, more than 30 human cases were caused by CFB bites in Zhejiang Province. In this paper, based on the reported data of the human rabies caused by both dogs and CFB in Zhejiang Province, we propose a multi-host zoonotic model for the dog-CFB-human transmission of rabies. We first evaluate the basic reproduction number R_0, discuss the stability of the disease-free equilibrium, and study persistence of the disease. Then we use our model to fit the reported data in Zhejiang Province from 2004 to 2017 and forecast the trend of human or livestock rabies. Finally by carrying out sensitivity analysis of the basic reproduction number in terms of parameters, we find that the transmission between dogs and CFB, the quantity of dogs, and the vaccination rate of dogs play important roles in the transmission of rabies. Our study suggests that rabies control and prevention strategies should include public education and awareness about rabies, increasing dog vaccination rate, reducing the dog and CFB interactions, and avoiding CFB bites or contact.

Key words: Rabies · Chinese ferret badgers · multi-host zoonotic SEIR model · Basic reproduction number · Vaccination

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1 Introduction

Rabies is an acute and dangerous zoonotic disease and causes almost 60,000 deaths worldwide per year (Fooks et al. [17], Lozano et al. [28]). Rabies virus is transmitted through the bite or scratch of a rabid animal (WHO [43]), where dogs are the main carrier of rabies and are responsible for most of the human rabies deaths worldwide (CDC [8]).

Rabies has been one of the most important infectious diseases in China since the 1950s. Although many preventive measures have been taken in past decades (including dog vaccination and postexposure prophylaxis following human exposure), rabies remains a significant public health problem in mainland China. Indeed, China is the second most country in the number of people killed by rabies worldwide, and the epidemic area has expanded to almost the entire country (Wang et al. [39]).

It is estimated that 95% of human rabies cases are due to dog bites in mainland China (Ministry of Health of the People's Republic of China (MOHC) [30]). However, in the last two decades the number of wildlife rabies and wildlife-associated human and livestock rabies cases has increased significantly, particularly in the southeast and northeast regions of China. Rabies viruses have been isolated or detected in wildlife, including the bat, Chinese ferret badger, raccoon, deer, vole, and wolf (Wang et al. [39]).

The Chinese ferret badger (CFB) lives mainly in southeastern China and has several names in southern China: crab-eating mongoose, rice field dog, viviparid-eating dog, loach-eating dog, and white face weasel, mainly because of their omnivorous behavior and external appearance. CFB-associated human rabies cases in China were emerged in 1994 (Shi et al. [34]). During that year, 6 patients with clinical signs of rabies received a preliminary diagnosis at Huzhou Second Hospital, Huzhou, Zhejiang Province. In 1995, a similar case was reported in the same hospital. Among the 7 case-patients, 6 were reported to have been bitten on the hands by CFBs. This was the first alleged epizootic of CFB-associated human rabies. From 1999 through 2003, 4 CFB-associated human rabies cases were reported in Huzhou, Zhejiang Province and 14 cases were reported in Hangzhou, both in Zhejiang Province (Gong et al. [18], Wang et al. [41]). In 2004, 1 human case in Huzhou and 3 human cases in Hangzhou were recorded (Fang et al. [16], Wang et al. [40]). Gong et al. [19] reported 7 rural residents of Coteau County in western Zhejiang Province died of rabies following badger bites. From 1994 to 2004, 12 of 20 human rabies cases in Huzhou and of 22 human rabies cases in Hangzhou were associated with CFB exposure (Zhang et al. [48]). The CFB-associated rabies patients have included CFB hunters who capture and sell CFBs, farmers with occasional exposure to sick CFBs, and residents exposed to sick CFBs in their yard or house. Currently, CFB trading and the consumption of its meat are common in the southeast areas of China, resulting in a frequent source of CFB bites or contact with humans.

Mathematical models have been used to analyze the epidemiological characteristics of rabies and can provide useful control measures. Since Anderson et al. [4] firstly proposed a deterministic model consisting of three subclasses, susceptible, infectious and recovered, to explain epidemiological features of rabies in fox populations in Europe, various models have been used to study different aspects of rabies in wild animals ([3, 5, 10, 13, 24, 35]). Recently there have been some studies on modeling canine and human rabies ([7, 20, 51]). In a very lately paper, Ruan [32] provided a review about the models, results, and simulations that team team has obtained recently on studying the transmission of rabies in China ([45, 22, 46, 47, 9]) and summarized the prevention and control measures for the spread of rabies in mainland China that were proposed based on these studies.

Many pathogens can infect multiple and highly diverse species (Woolhouse et al. [42]), including wildlife species (Dobson [14]), and the transmission of infectious diseases can be affected by the host diversity (Ostfeld and Keesing [31]). Examples include bovine-tuberculosis (infecting badges and cattle) and foot-and-mouth disease (infecting cattle, sheep, and pigs) (Keeling and Rohani [25]).

Holt and Pickering [21], Begon and Bowers [6] and Allen and Cormier [2] studied two-host SIS epidemic models. Dobson [14], Keeling and Rohani [25], McCormack and Allen [29] investigated multi-host SIR epidemic models. Recent study [39] shows that CFBs, as a kind of wildlife, have formed independent rabies enzootics during long-term rabies infestation and may constitute wildlife reservoirs responsible for the independent maintenance of rabies viruses in mainland China, and could play a role in human or livestock rabies. In order to explore the effect of wildlife, especially CFBs, on human and livestock rabies, it is necessary to consider a model for the spread of rabies virus between dogs and CFBs, and from both to humans. As far as we know, there are very few relative studies (Allen et al. [1], Lloyd-Smith et al. [27]).

In this paper, in order to better understand wildlife rabies and its effect on human and livestock rabies, based on the reported data and characteristics of the rabies infection in Zhejiang Province, we propose a multi-host zoonotic SEIR model for the dog-CFB-human transmission of rabies. We first determine the basic reproduction number R_0 and discuss the global stability of the disease-free equilibrium and persistence of the disease. Then we use our model to fit the reported data in Zhejiang Province from 2004 to 2017 and forecast the trend of human or livestock rabies. Finally by carrying out sensitivity analysis of the basic reproduction number in terms of parameters, we find that the transmission between dogs and CFB, the quantity of dogs, and the vaccination rate of dogs play important roles in the transmission of rabies. Our study suggests that rabies control and prevention strategies should include public education and awareness about rabies, increasing the dog vaccination rate, reducing the contact with CFB and reduction of the dog and CFB population.

This paper is organized as follows. In section 2, we propose a deterministic model and present some fundamental analysis of the model. In section 3, we use the model to fit the reported data in Zhejiang Province from 2004 to 2017 and carry out some numerical simulations. The paper ends with a brief discussion in section 4.

2 Mathematical Modeling and Analysis

2.1 Model Formulation

To model the transmission of rabies virus between dogs, CFBs, and humans, we classify each of dog and human populations into four subclasses: susceptible, exposed, infectious and recovered; and let $S_d(t), E_d(t), I_d(t), R_d(t)$ and $S_h(t), E_h(t), I_h(t), R_h(t)$ denote the densities of susceptible, exposed, infective, recovered dog and human populations at time t, respectively. The CFB population is classified into three subclasses: susceptible, exposed, infectious, and are denoted by $S_c(t), E_c(t), I_c(t)$ at times t, respectively. The 11 compartments and model variables are given in Figure 2.1.

It is assumed that dogs and CFBs can transmit the virus to themselves and to each other, both infected dogs and CFBs can spread the rabies virus to humans via contact, and humans do not spread the virus any further. Our assumptions on the dynamical transmission of rabies among dogs, CFBs and human populations are presented in the flowchart in Figure 2.1. The model is a

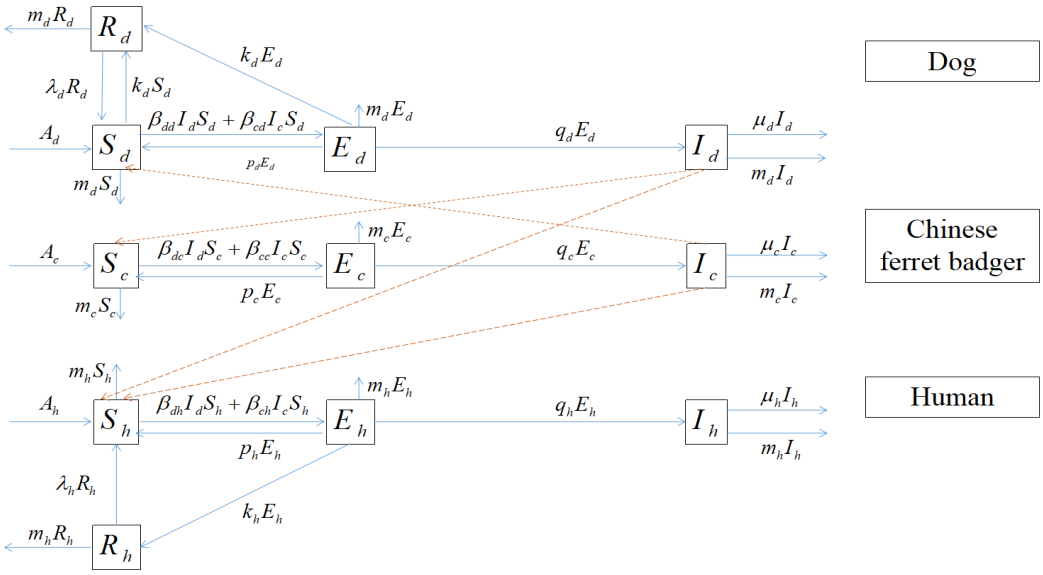


Figure 2.1: Transmission diagram of rabies among dogs, CFBs, and humans

system of eleven ordinary differential equations:

$$\begin{cases} \frac{\mathrm{d}S_d}{\mathrm{d}t} = A_d + \lambda_d R_d + p_d E_d - \beta_{dd} I_d S_d - \beta_{cd} I_c S_d - (m_d + k_d) S_d, \\ \frac{\mathrm{d}E_d}{\mathrm{d}t} = \beta_{dd} I_d S_d + \beta_{cd} I_c S_d - (m_d + k_d + p_d + q_d) E_d, \\ \frac{\mathrm{d}I_d}{\mathrm{d}t} = q_d E_d - (m_d + \mu_d) I_d, \\ \frac{\mathrm{d}R_d}{\mathrm{d}t} = k_d (S_d + E_d) - (m_d + \lambda_d) R_d, \\ \frac{\mathrm{d}S_c}{\mathrm{d}t} = A_c + p_c E_c - \beta_{dc} I_d S_c - \beta_{cc} I_c S_c - m_c S_c, \\ \frac{\mathrm{d}E_c}{\mathrm{d}t} = \beta_{dc} I_d S_c + \beta_{cc} I_c S_c - (m_c + p_c + q_c) E_c, \\ \frac{\mathrm{d}I_c}{\mathrm{d}t} = q_c E_c - (m_c + \mu_c) I_c, \\ \frac{\mathrm{d}S_h}{\mathrm{d}t} = A_h + \lambda_h R_h + p_h E_h - \beta_{dh} I_d S_h - \beta_{ch} I_c S_h - m_h S_h, \\ \frac{\mathrm{d}E_h}{\mathrm{d}t} = \beta_{dh} I_d S_h + \beta_{ch} I_c S_h - (m_h + k_h + p_h + q_h) E_h, \\ \frac{\mathrm{d}I_h}{\mathrm{d}t} = q_h E_h - (m_h + \mu_h) I_h, \\ \frac{\mathrm{d}R_h}{\mathrm{d}t} = k_h E_h - (m_h + \lambda_h) R_h. \end{cases} \tag{2.1}$$

The parameters are described in Table 1.

2.2 Extinction and uniformly persistence of the disease

In this section we discuss the disease-free equilibrium and uniform persistence of model (2.1). Notice that from model (2.1) we have

$$\begin{cases} \frac{\mathrm{d}N_d}{\mathrm{d}t} = A_d - m_d N_d - \mu_d I_d, \\ \frac{\mathrm{d}N_c}{\mathrm{d}t} = A_c - m_c N_c - \mu_c I_c, \\ \frac{\mathrm{d}N_h}{\mathrm{d}t} = A_h - m_h N_h - \mu_h I_h. \end{cases} \tag{2.2}$$

Let

$$\Lambda = \{(S_d, E_d, I_d, R_d, S_c, E_c, I_c, S_h, E_h, I_h, R_h) \mid S_d > 0, E_d \geq 0, I_d \geq 0, R_d > 0,$$
$$S_c > 0, E_c \geq 0, I_c \geq 0, S_h > 0, E_h \geq 0, I_h \geq 0, R_h > 0, 0 < S_d + E_d + I_d + R_d < \frac{A_d}{m_d},$$

Table 1: Parameters of model (2.1).

Para	Value	Unit	Interpretation	Source
A_d	7.7×10^5	year^{-1}	dog recruitment rate	[45]
m_d	0.11	year^{-1}	dog natural mortality rate	[45]
λ_d	0.5	year^{-1}	dog loss rate of vaccination immunity	[45]
k_d	0.24	year^{-1}	dog vaccination rate	assumption
p_d	0.37	year^{-1}	rate of no clinical outcome of exposed dogs	[45]
q_d	0.37	year^{-1}	rate of clinical outcome of exposed dogs	[45]
μ_d	1	year^{-1}	dog disease-related death rate	[45]
β_{dd}	6.5×10^{-7}	year^{-1}	dog-to-dog transmission rate	fitting
β_{cd}	4.885×10^{-7}	year^{-1}	CFB-to-dog transmission rate	fitting
A_c	10^4	year^{-1}	CFB recruitment rate	assumption
m_c	0.11	year^{-1}	CFB natural mortality rate	assumption
p_c	0.35	year^{-1}	rate of no clinical outcome of exposed CFB	assumption
q_c	0.35	year^{-1}	rate of clinical outcome of exposed CFB	assumption
μ_c	1	year^{-1}	CFB disease-related death rate	assumption
β_{dc}	4.885×10^{-7}	year^{-1}	dog-to-CFB transmission rate	fitting
β_{cc}	6.3×10^{-8}	year^{-1}	CFB-to-CFB transmission rate	fitting
A_h	5×10^6	year^{-1}	human annual birth population	[50]
m_h	0.0056	year^{-1}	human natural mortality rate	[50]
λ_h	1	year^{-1}	human loss rate of vaccination immunity	[22]
k_h	0.328	year^{-1}	human vaccination rate	[45]
p_h	0.33	year^{-1}	rate of no clinical outcome of exposed humans	[45]
q_h	0.33	year^{-1}	rate of clinical outcome of exposed humans	[45]
μ_h	1	year^{-1}	human disease-related death rate	[30]
β_{dh}	3.8×10^{-10}	year^{-1}	dog-to-human transmission rate	fitting
β_{ch}	3.8×10^{-11}	year^{-1}	CFB-to-human transmission rate	fitting

$$0 < S_c + E_c + I_c < \frac{A_c}{m_c}, 0 < S_h + E_h + I_h + R_h < \frac{A_h}{m_h} \Bigg\}.$$

We have the following results.

Theorem 2.1 *The region Λ is positively invariant with respect to system (2.1). In particular, $(S_d(t), E_d(t), I_d(t), R_d(t), S_c(t), E_c(t), I_c(t), S_h(t), E_h(t), I_h(t), R_h(t))$ is nonnegative for all $t > 0$ if the initial values satisfy $S_d(0) \geq 0, E_d(0) \geq 0, I_d(0) \geq 0, R_d(0) \geq 0, S_c(0) \geq 0, E_c(0) \geq 0, I_c(0) \geq 0, S_h(0) \geq 0, E_h(0) \geq 0, I_h(0) \geq 0, R_h(0) \geq 0$.*

Proof. On the nonnegativity of solutions of model (2.1) with nonnegative initial conditions, by the continuous dependence of solutions with respect to initial values, we only need to show that $(S_d(t), E_d(t), I_d(t), R_d(t), S_c(t), E_c(t), I_c(t), S_h(t), E_h(t), I_h(t), R_h(t))$ is positive for all $t > 0$ when $S_d(0) > 0, E_d(0) > 0, I_d(0) > 0, R_d(0) > 0, S_c(0) > 0, E_c(0) > 0, I_c(0) > 0, S_h(0) > 0, E_h(0) > 0, I_h(0) > 0$ and $R_h(0) > 0$. Let

$$n(t) = \min\left\{S_d(t), E_d(t), I_d(t), R_d(t), S_c(t), E_c(t), I_c(t), S_h(t), E_h(t), I_h(t), R_h(t)\right\}, \forall t > 0.$$

Clearly, $n(0) > 0$. Assuming that there exists a $t_1 > 0$ such that $n(t_1) = 0$ and $n(t) > 0, \forall t \in [0, t_1)$.

If $n(t_1) = S_d(t_1)$, due to the first equation of model (2.1), we obtain that

$$\frac{\mathrm{d}S_d}{\mathrm{d}t} \geqslant -\beta_{dd} I_d S_d - \beta_{cd} I_c S_d - (m_d + k_d) S_d, \quad \forall t > [0, t_1],$$

then

$$0 = S_d(t_1) \geqslant S_d(0) e^{-\int_0^{t_1} (\beta_{dd} I_d(t) + \beta_{cd} I_c(t) + m_d + k_d) \mathrm{d}s} > 0,$$

which leads to a contradiction.

If $n(t_1) = E_d(t_1)$, since $I_d(t) \geq 0$ and $S_d(t) \geq 0$ for all $t \in [0, t_1]$, from the second equation of model (2.1), it follows that

$$\frac{\mathrm{d}E_d}{\mathrm{d}t} \geqslant -(p_d + q_d + k_d + m_d) E_d, \quad \forall t > [0, t_1],$$

then

$$0 = E_d(t_1) \geqslant E_d(0) e^{-(p_d + q_d + k_d + m_d) t_1} > 0,$$

which also leads to a contradiction.

Similarly, we can show that $S_d(t) > 0, E_d(t) > 0, I_d(t) > 0, R_d(t) > 0, S_c(t) > 0, E_c(t) > 0, I_c(t) > 0, S_h(t) > 0, E_h(t) > 0, I_h(t) > 0, R_h(t) > 0$ for all $t > 0$.

Concerning (2.2), let $N_d(t) = S_d(t) + E_d(t) + I_d(t) + R_d(t)$, we have

$$\frac{\mathrm{d}N_d}{\mathrm{d}t} \leqslant A_d - m_d N_d,$$

which implies that $N_d(t) \leqslant \frac{A_d}{m_d} + N_d(0) e^{-m_d t}$, where $N_d(0) = S_d(0) + E_d(0) + I_d(0) + R_d(0)$. Hence, $N_d(t)$ is bounded for all $t \geqslant 0$ and

$$\limsup_{t \to \infty} N_d(t) = \frac{A_d}{m_d},$$

which implies that $S_d(t)$, $E_d(t)$, $I_d(t)$ and $R_d(t)$ are also bounded for all $t > 0$.

Set $N_c(t) = S_c(t) + E_c(t) + I_c(t)$ and $N_t(t) = S_t(t) + E_h(t) + I_h(t) + R_h(t)$, from the last two equation of system (2.2), similar to $N_d(t)$, we can obtain

$$\limsup_{t \to \infty} N_c(t) = \frac{A_c}{m_c}, \limsup_{t \to \infty} N_h(t) = \frac{A_h}{m_h},$$

which means that $S_c(t)$, $E_c(t)$, $I_c(t)$, $S_h(t)$, $E_h(t)$, $I_h(t)$ and $R_h(t)$ are bounded for $t > 0$. This completes the proof. ∎

Model (2.1) always has a disease-free equilibrium

$$P_0 = \left(\hat{S}_d, 0, 0, \hat{R}_d, \hat{S}_c, 0, 0, \hat{S}_h, 0, 0, 0\right),$$

where

$$\hat{S}_d = \frac{A_d(m_d + \lambda_d)}{m_d(m_d + \lambda_d + k_d)},\ \hat{R}_d = \frac{A_d k_d}{m_d(m_d + \lambda_d + k_d)},\ \hat{S}_c = \frac{A_c}{m_c}, \hat{S}_h = \frac{A_h}{m_h}.$$

Following the notations and method of Diekmann et al. [11, 12] and van den Driessche and Watmough [38], we obtain the basic reproduction number R_0 as follows:

$$R_0 = \frac{1}{2}\left(H_1\beta_{dd} + H_2\beta_{cc} + \sqrt{(H_1\beta_{dd} - H_2\beta_{cc})^2 + 4H_1H_2\beta_{cd}\beta_{dc}}\right),$$

where

$$H_1 = \frac{q_d\hat{S}_d}{(m_d + k_d + p_d + q_d)(m_d + \mu_d)},\ H_2 = \frac{q_c\hat{S}_c}{(m_c + p_c + q_c)(m_c + \mu_c)}.$$

The first term in R_0 can be expressed as

$$H_1\beta_{dd} = \frac{\beta_{dd}\hat{S}_d}{(m_d + k_d + p_d + q_d)}\frac{q_d}{(m_d + \mu_d)},$$

which means that near the disease-free equilibrium an infective dog causes $\beta_{dd}\hat{S}_d$ new infections in a unit time, the mean time spent in the exposed compartment is $\frac{1}{m_d+k_d+p_d+q_d}$, and the mean time spend in the infective compartment is $\frac{q_d}{m_d+\mu_d}$. Similar interpretations can be given for the second term (for the CFBs) and third term (for the interactions between dogs and CFBs), and the square root arises from the two generations required for an infected dog or CFB to reproduce itself. The factor $\frac{1}{2}$ means that the rabies virus can be transmitted only from dogs and CFBs to humans but not vice versa.

We can verify that model (2.1) satisfies the conditions $(A1) - (A5)$ given in van den Driessche and Watmough [38]. By Theorem 2 in van den Driessche and Watmough [38], we have the locally asymptotical stability of the disease-free equilibrium P_0 for model (2.1). Moreover, we obtain the following results about the global asymptotical stability of the disease-free equilibrium P_0 for model (2.1).

Theorem 2.2 *The disease-free equilibrium P_0 is globally asymptotically stable when $R_0 < 1$.*

Proof. Because the last four equations are independent of the first seven equations, we consider the first seven equations as follows

$$\begin{cases} \frac{\mathrm{d}S_d}{\mathrm{d}t} = A_d + \lambda_d R_d + p_d E_d - \beta_{dd} I_d S_d - \beta_{cd} I_c S_d - (m_d + k_d)\, S_d, \\ \frac{\mathrm{d}E_d}{\mathrm{d}t} = \beta_{dd} I_d S_d + \beta_{cd} I_c S_d - (m_d + k_d + p_d + q_d)\, E_d, \\ \frac{\mathrm{d}I_d}{\mathrm{d}t} = q_d E_d - (m_d + \mu_d)\, I_d, \\ \frac{\mathrm{d}R_d}{\mathrm{d}t} = k_d\,(S_d + E_d) - (m_d + \lambda_d)\, R_d, \\ \frac{\mathrm{d}S_c}{\mathrm{d}t} = A_c + p_c E_c - \beta_{dc} I_d S_c - \beta_{cc} I_c S_c - m_c S_c, \\ \frac{\mathrm{d}E_c}{\mathrm{d}t} = \beta_{dc} I_d S_c + \beta_{cc} I_c S_c - (m_c + p_c + q_c)\, E_c, \\ \frac{\mathrm{d}I_c}{\mathrm{d}t} = q_c E_c - (m_c + \mu_c)\, I_c. \end{cases} \tag{2.3}$$

Considering the first two equations of system (2.3), we observe that

$$\begin{aligned}\frac{\mathrm{d}\left(S_d+E_d\right)}{\mathrm{d}t} &= A_d+\lambda_d R_d-\left(m_d+k_d\right)\left(S_d+E_d\right)-q_d E_d \\ &\leqslant A_d+\frac{\lambda_d A_d}{m_d}-\left(m_d+k_d+\lambda_d\right)\left(S_d+E_d\right)-q_d E_d-\lambda_d I_d \\ &\leqslant A_d+\frac{\lambda_d A_d}{m_d}-\left(m_d+k_d+\lambda_d\right)\left(S_d+E_d\right).\end{aligned} \tag{2.4}$$

Thus,

$$\limsup_{t\to\infty}\left(S_d+E_d\right)=\frac{A_d\left(m_d+\lambda_d\right)}{m_d\left(m_d+k_d+\lambda_d\right)}=\hat{S}_d.$$

Since $E_d \geqslant 0$, it is easy to see that

$$\limsup_{t\to\infty} S_d=\frac{A_d\left(m_d+\lambda_d\right)}{m_d\left(m_d+k_d+\lambda_d\right)}=\hat{S}_d.$$

From the fifth and sixth equations of model (2.3), we have

$$\frac{\mathrm{d}\left(S_c+E_c\right)}{\mathrm{d}t}=A_c-q_c E_c-m_c\left(S_c+R_c\right)\leqslant A_c-m_c\left(S_c+E_c\right).$$

Because $E_c \geqslant 0$, it follows that

$$\limsup_{t\to\infty} S_c=\frac{A_c}{m_c}=\hat{S}_c.$$

Hence, we have proved that $S_d \leqslant \hat{S}_d$ and $S_c \leqslant \hat{S}_c$.

According to system (2.3), we also know that

$$\begin{cases}\frac{\mathrm{d}E_d}{\mathrm{d}t} \leqslant \beta_{dd} I_d \hat{S}_d+\beta_{cd} I_c \hat{S}_d-\left(m_d+k_d+p_d+q_d\right) E_d, \\ \frac{\mathrm{d}I_d}{\mathrm{d}t}=q_d E_d-\left(m_d+\mu_d\right) I_d, \\ \frac{\mathrm{d}E_c}{\mathrm{d}t} \leqslant \beta_{dc} I_d \hat{S}_c+\beta_{cc} I_c \hat{S}_c-\left(m_c+p_c+q_c\right) E_c, \\ \frac{\mathrm{d}I_c}{\mathrm{d}t}=q_c E_c-\left(m_c+\mu_c\right) I_c\end{cases} \tag{2.5}$$

for $t>0$. Consider the following auxiliary system

$$\begin{cases}\frac{\mathrm{d}\tilde{E}_d}{\mathrm{d}t}=\beta_{dd}\hat{S}_d\tilde{I}_d+\beta_{cd}\hat{S}_d\tilde{I}_c-\left(m_d+k_d+p_d+q_d\right)\tilde{E}_d, \\ \frac{\mathrm{d}\tilde{I}_d}{\mathrm{d}t}=q_d\tilde{E}_d-\left(m_d+\mu_d\right)\tilde{I}_d, \\ \frac{\mathrm{d}\tilde{E}_c}{\mathrm{d}t}=\beta_{dc}\hat{S}_c\tilde{I}_d+\beta_{cc}\hat{S}_c\tilde{I}_c-\left(m_c+p_c+q_c\right)\tilde{E}_c, \\ \frac{\mathrm{d}\tilde{I}_c}{\mathrm{d}t}=q_c\tilde{E}_c-\left(m_c+\mu_c\right)\tilde{I}_c.\end{cases} \tag{2.6}$$

Since $R_0<1$, we conclude that the equilibrium $(0,0,0,0)$ of system (2.6) is a global attractor. From the comparison principle, it is easy to see that $\lim_{t\to+\infty} E_d=\lim_{t\to+\infty} E_c=\lim_{t\to+\infty} I_d=\lim_{t\to+\infty} I_c=0$. Therefore, the limiting affine system of (2.3) is

$$\begin{cases}\frac{\mathrm{d}S_d}{\mathrm{d}t}=A_d+\lambda_d R_d-\left(m_d+k_d\right)S_d, \\ \frac{\mathrm{d}R_d}{\mathrm{d}t}=k_d S_d-\left(m_d+\lambda_d\right)R_d, \\ \frac{\mathrm{d}S_c}{\mathrm{d}t}=A_c-m_c S_c.\end{cases} \tag{2.7}$$

We can show that the positive equilibrium $\left(\hat{S}_d,\hat{R}_d,\hat{S}_c\right)$ of (2.7) is globally asymptotically stable, so $\lim_{t\to+\infty} S_d=\hat{S}_d$, $\lim_{t\to+\infty} R_d=\hat{R}_d$ and $\lim_{t\to+\infty} S_c=\hat{S}_c$. Applying the theory of asymptotically autonomous system in [37], the equilibrium $\left(\hat{S}_d,0,0,\hat{R}_d,\hat{S}_c,0,0\right)$ of model (2.3) is globally asymptotically stable when $R_0<1$.

Next, we consider the last four equation

$$\begin{cases} \frac{\mathrm{d}S_h}{\mathrm{d}t} = A_h + \lambda_h R_h + p_h E_h - \beta_{dh} I_d S_h - \beta_{ch} I_c S_h - m_h S_h, \\ \frac{\mathrm{d}E_h}{\mathrm{d}t} = \beta_{dh} I_d S_h + \beta_{ch} I_c S_h - (m_h + k_h + p_h + q_h) E_h, \\ \frac{\mathrm{d}I_h}{\mathrm{d}t} = q_h E_h - (m_h + \mu_h) I_h, \\ \frac{\mathrm{d}R_h}{\mathrm{d}t} = k_h E_h - (m_h + \lambda_h) R_h. \end{cases} \tag{2.8}$$

Note that if $I_d \to 0$, $I_c \to 0$ if $t \to +\infty$, the limiting system of (2.8) is

$$\frac{\mathrm{d}S_h}{\mathrm{d}t} = A_h - m_h S_h. \tag{2.9}$$

We obtain that the disease-free equilibrium $\left(\hat{S}_h, 0, 0, 0\right)$ of the limiting system is globally asymptotically stable. By using the theory of asymptotically autonomous systems [37] once again, we know that $\left(\hat{S}_h, 0, 0, 0\right)$ is also the disease-free equilibrium of (2.8) and is globally asymptotically stable. Hence, the disease-free equilibrium P_0 is globally asymptotically stable in the region Λ when $R_0 < 1$. ■

We then discuss the uniform persistence of system (2.1) when $R_0 > 1$. We first consider the first seven equations of the model (2.1)

$$\begin{cases} \frac{\mathrm{d}S_d}{\mathrm{d}t} = A_d + \lambda_d R_d + p_d E_d - \beta_{dd} I_d S_d - \beta_{cd} I_c S_d - (m_d + k_d) S_d, \\ \frac{\mathrm{d}E_d}{\mathrm{d}t} = \beta_{dd} I_d S_d + \beta_{cd} I_c S_d - (m_d + k_d + p_d + q_d) E_d, \\ \frac{\mathrm{d}I_d}{\mathrm{d}t} = q_d E_d - (m_d + \mu_d) I_d, \\ \frac{\mathrm{d}R_d}{\mathrm{d}t} = k_d (S_d + E_d) - (m_d + \lambda_d) R_d, \\ \frac{\mathrm{d}S_c}{\mathrm{d}t} = A_c + p_c E_c - \beta_{dc} I_d S_c - \beta_{cc} I_c S_c - m_c S_c, \\ \frac{\mathrm{d}E_c}{\mathrm{d}t} = \beta_{dc} I_d S_c + \beta_{cc} I_c S_c - (m_c + p_c + q_c) E_c, \\ \frac{\mathrm{d}I_c}{\mathrm{d}t} = q_c E_c - (m_c + \mu_c) I_c. \end{cases} \tag{2.10}$$

Let

$$\begin{aligned} \Lambda_1 = \{(S_d, E_d, I_d, R_d, S_c, E_c, I_c) \mid S_d > 0, E_d \geq 0, I_d \geq 0, R_d > 0, S_c > 0, E_c \geq 0, I_c \geq 0, \\ 0 < S_d + E_d + I_d + R_d < \frac{A_d}{\mu_d}, 0 < S_c + E_c + I_c < \frac{A_c}{\mu_c}\Big\} \subseteq \Lambda \end{aligned}$$

and $\partial\Lambda_1$ be the boundary of Λ_1. Let $\Phi_t(x) = \Phi(t, x(t))$ be the flow on Λ_1 generated by the solution $x(t)$ of model (2.10) with initial condition $x(0) = (S_d(0), E_d(0), I_d(0), R_d(0), S_c(0), E_c(0), I_c(0)) \in \Lambda_1$.

Theorem 2.3 *If $R_0 > 1$, then the flow $\Phi_t(x)$ on Λ_1 is uniformly persistent for any solution $x(t)$ with $S_d > 0$,$R_d > 0$,$S_c > 0$ and $E_d > 0$,$I_d > 0$ or $E_c > 0$,$I_c > 0$.*

Proof. Let

$$\Omega = \bigcup_{y \in Y} \omega(y),$$

where

$$\omega(y) = \bigcap_{t \geqslant 0} \overline{\Phi\left([t, \infty) \times \{y\}\right)}$$

and

$$Y = \left\{x = (S_d, E_d, I_d, R_d, S_c, E_c, I_c) \mid \Phi_t(x) \in \partial\Lambda_1, \forall t > 0\right\}.$$

We can see that Ω is the maximal invariant set of $\Phi_t(x)$ on $\partial\Lambda_1$. By analyzing the system (2.10), we obtain that Ω consists of a unique equilibrium $P_{00}\left(\hat{S}_d, 0, 0, \hat{R}_d, \hat{S}_c, 0, 0\right)$ on the boundary of Λ_1. Hence, $\{P_{00}\}$ represents an acyclic covering for Ω.

We analyze the behavior of any solution $x(t)$ of model (2.10) close to P_{00}. We classify the initial conditions into two cases.

(1) If $I_d(0) = E_d(0) = I_c(0) = E_c(0) = 0$, then $I_d(t) = E_d(t) = I_c(t) = E_c(t) = 0$. From system (2.10), we can see that $(S_d(t), 0, 0, R_d(t), S_c(t), 0, 0)$ tends to P_{00} as $t \to +\infty$.

(2) If $E_d(0), I_d(0) > 0$ or $E_c(0), I_c(0) > 0$, then $E_d(t), I_d(t) \geqslant 0$ or $E_c(t), I_c(t) \geqslant 0$ for all $t > 0$ by Theorem 2.1. If $x(t)$ is close to P_{00}, according to system (2.10) there is some ρ such that

$$\begin{cases} \frac{\mathrm{d}E_d}{\mathrm{d}t} > \tilde{a}_{11}E_d + 0 + \tilde{a}_{13}I_d + \tilde{a}_{14}I_c, \\ \frac{\mathrm{d}E_c}{\mathrm{d}t} > 0 + \tilde{a}_{22}E_c + \tilde{a}_{23}I_d + \tilde{a}_{24}I_c, \\ \frac{\mathrm{d}I_d}{\mathrm{d}t} > \tilde{a}_{31}E_d + 0 + \tilde{a}_{33}I_d + 0, \\ \frac{\mathrm{d}I_c}{\mathrm{d}t} > 0 + \tilde{a}_{42}E_c + 0 + \tilde{a}_{44}I_c, \end{cases} \tag{2.11}$$

where $\tilde{a}_{11} = -(m_d + p_d + q_c + k_d + \rho)$, $\tilde{a}_{13} = \beta_{dd}\hat{S}_d - \rho$, $\tilde{a}_{14} = \beta_{cd}\hat{S}_d - \rho$, $\tilde{a}_{22} = -(m_c + p_c + q_c + \rho)$, $\tilde{a}_{23} = \beta_{dc}\hat{S}_c - \rho$, $\tilde{a}_{24} = \beta_{cc}\hat{S}_c - \rho$, $\tilde{a}_{31} = q_d - \rho$, $\tilde{a}_{33} = -(m_d + \mu_d + \rho)$, $\tilde{a}_{42} = q_c - \rho$, $\tilde{a}_{44} = -(m_c + \mu_c + \rho)$, and the largest eigenvalue of the coefficient matrix $\tilde{A}(\tilde{a}_{ij})$ in (2.11) is positive because of $R_0 > 1$ (Diekmann et al. [11, 12]). Hence, the solutions of the linear quasi-monotonic system

$$\begin{cases} \frac{\mathrm{d}x_0}{\mathrm{d}t} = \tilde{a}_{11}x_0 + 0 + \tilde{a}_{13}y_0 + \tilde{a}_{14}y_1, \\ \frac{\mathrm{d}x_1}{\mathrm{d}t} = 0 + \tilde{a}_{22}x_1 + \tilde{a}_{23}y_0 + \tilde{a}_{24}y_1, \\ \frac{\mathrm{d}y_0}{\mathrm{d}t} = \tilde{a}_{31}x_0 + 0 + \tilde{a}_{33}y_0 + 0, \\ \frac{\mathrm{d}y_1}{\mathrm{d}t} = 0 + \tilde{a}_{42}x_1 + 0 + \tilde{a}_{44}y_1 \end{cases} \tag{2.12}$$

with positive initial values are exponentially increasing as $t \to \infty$. By applying the comparison principle, we can see that (E_d, E_c, I_d, I_c) goes away from $(0, 0, 0, 0)$ if $t \to \infty$. Therefore, $\{P_{00}\}$ is an isolated invariant set of the flow $\Phi_t(x)$. By Theorem 4.3 in Freedman et al. [15], model (2.10) is uniformly persistent if $R_0 > 1$. This completes the proof. ■

Remark 2.4 The semiflow $\Phi_t(x)$ defined above is point dissipative, all solutions of the system are ultimately bounded in Λ_1, and the disease is uniformly persistent if $R_0 > 1$ from Theorem 2.3. Thus, it is easy to see that system (2.1) has at least one positive equilibrium P^* (see the result in Hutson and Schmitt [23] or Zhao [49]). However, it is difficult to express P^* explicitly and determine its stability because the model (2.1) consists of 11 equations.

3 Numerical Simulations and Sensitivity Analysis

In this section, we use model (2.1) to simulate the reported human rabies data from Zhejiang Province, China, and carry out some sensitivity analyses on some parameters.

From the Department of Health of Zhejiang Province and [36], we obtained the data on human rabies cases which is shown in Table 2. According to [39], the numbers of CFB-originated human rabies in Zhejiang Province are shown in Table 3. Most parameter values can be obtained from the literature or by estimation. We estimate β_{dd}, β_{cd}, β_{cc}, β_{dc}, β_{dh} and β_{ch} by using the least-square fitting of $I_h(t_i)$ through discretizing the ordinary differential system (2.1) as follows

$$I_h(t_i + \Delta t) = (q_h E_h(t_i) - \mu_d I_d(t_i) - m_d I_d(t_i))\,\Delta t + I_h(t_i).$$

The least-square fitting is to minimize the objective function

$$J(\theta) = \frac{1}{n}\sum_{i=1}^{n}(I_h(t_i) - \hat{I}_h(t_i))^2,$$

which is implemented by the instruction *lsqnonlin*, a part of the optimization toolbox in MATLAB.

Table 2: The data on human rabies cases in Zhejiang Province ([36]).

Year	2004	2005	2006	2007	2008	2009	2011	2011	2012	2013	2014	2015	2016	2017
Cases	74	61	58	57	38	31	25	18	14	8	9	8	18	14

The parameter values are listed in Table 1. In Zhejiang Province, it is estimated that there are about two million dogs on rabies exposure every year and the vaccination rate is only 0.328 or less from online news. Hence, we estimate that the number of vaccinated humans is 0.6 million, so $R_h(0) = 6 \times 10^5$; and from the data in 2004, we know that $I_h(0) = 74$; we make the data fitting to obtain that $E_h(0) = 300$, then $S_h(0) = 5.1 \times 10^7$; there are about three million dogs and four hundred thousand rabies vaccines every year, so we estimate that $S_d(0) = 2.4 \times 10^6$, $R_d(0) = 6 \times 10^5$ and assume that $E_d(0) = 2.9 \times 10^4$, $I_d(0) = 2 \times 10^4$, $S_c(0) = 10^5$, and data fitting gives $E_c(0) = 2084$, $I_c(0) = 1526$.

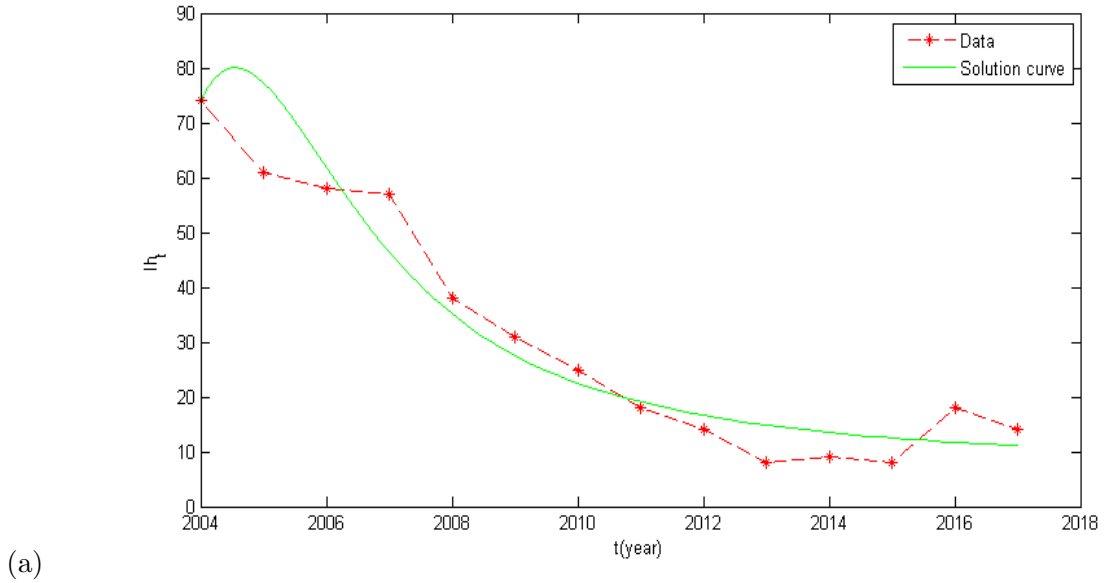
Table 3: The data of CFB-originated human rabies in Zhejiang Province ([39]).

Year	1994-1995	1996-2004	2006-2007	2008
Cases	15	36	2	2

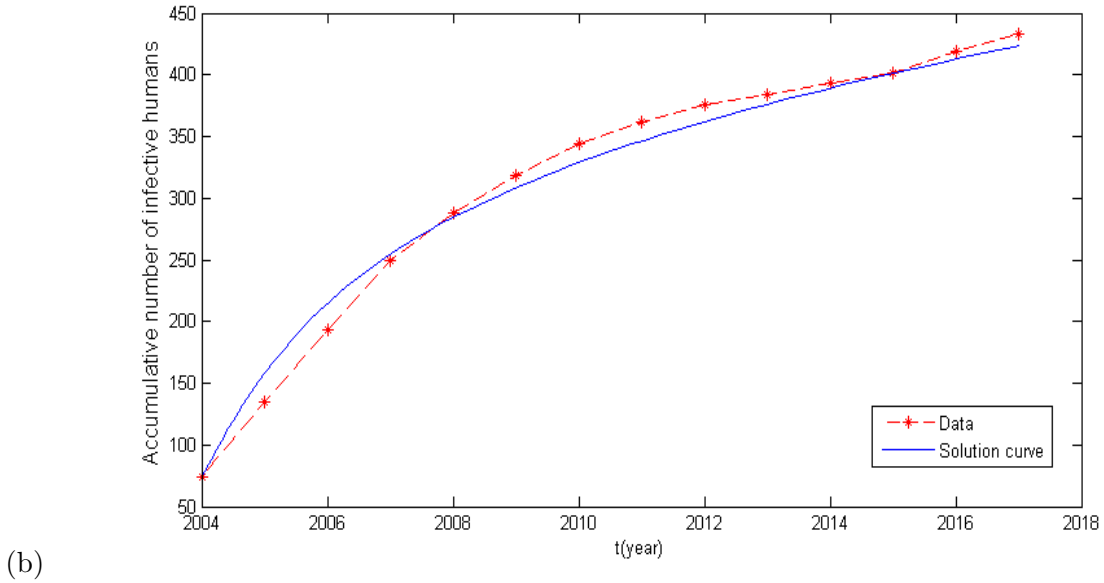
Based on the parameter values given in Table 1, we use model (2.1) to simulate the data from 2004 to 2017 and predict the trend of human rabies infections in Zhejiang Province. Figure 3.1 represents the simulation of our model with reasonable parameter values which provides a good match to the data on infected human rabies cases in Zhejiang Province from 2004 to 2017. In Figure 3.2 our model predicts that the number of human rabies infection will level off in the next a couple of years and then with increase after ten years under the current control measures. Using the simulated parameter values in Table 1, we compute that $R_0 = 1.0114$ in Zhejiang Province. Thus, with the current control and prevention measures, human rabies will persist in Zhejiang Province.

If we fix all parameters except β_{dd} (transmission rate from dogs to dogs) or β_{cc} (transmission rate from CFBs to CFBs), Figure 3.3(a) shows that the basic reproduction number R_0 increases sharply as β_{dd} increases, Figure 3.3(b) indicates that there is a upward trend of R_0 with the increase of β_{cc}, Figure 3.3(c) and (d) represents the relationship between R_0 and β_{dc} (the transmission rate from dogs to CFBs) and between R_0 and β_{cd} (the transmission rate from CFBs to dogs), respectively. We can see that the influence of the parameter β_{cc} on the basic reproduction number R_0 is less than that of the parameters β_{dd}, β_{dc}, and β_{cd}. So, reducing the transmission rate in dogs is an efficient way to decrease the basic reproduction number R_0. Figure 3.3(e) and Figure 3.3(f) show that the lower transmission rate between dogs and CFBs can also reduce R_0. Thus, decreasing the transmission rate between dogs and CFBs is also an important way to control rabies.

Figure 3.4(a) shows that the basic reproduction number R_0 can be less than 1 if A_d is less than 7.6×10^5. But the annual birth population of dogs can achieve 7.7×10^5 or more in Zhejiang Province. So if the birth number of dogs cannot be controlled under 7.6 million, other control measures have to be explored in oder to reduce the case of human rabies in Zhejiang Province. From Figure 3.4(b), it can be seen that k_d has an obvious effect on R_0, where R_0 is a concave function of k_d. This indicates that immunization is an effective measure to control rabies. Figure 3.4(c) describes the effect of A_c on R_0. Compared with the influence of A_d or k_d, A_c has less effect



(a)



(b)

Figure 3.1: Simulations of human rabies cases over time in Zhejiang Province of China. The smooth curves represent the solution $I_h(t)$ of model (2.1) and the dashed curves denote the reported human rabies cases from 2004 to 2017. (a) Using $I_h(t)$ to fit the annual data; (b) Fitting the accumulative numbers of infective human cases.

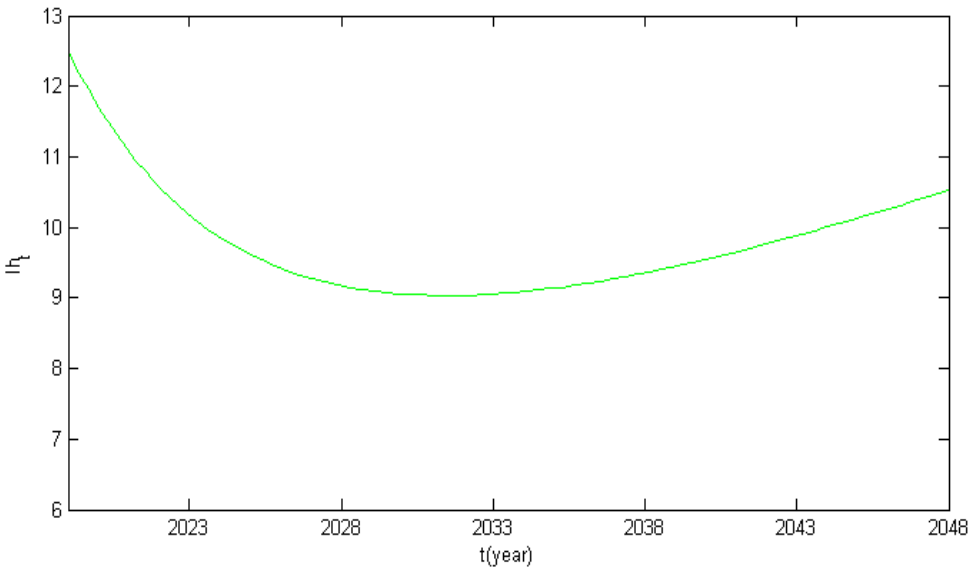


Figure 3.2: Prediction of human rabies cases in Zhejiang Province of China.

on the basic reproduction number R_0. Figure 3.4(d) shows the co-effect of (A_d, A_c) on R_0. It demonstrates that reducing the newborns of both dogs and CFBs is an effective means to control rabies infection.

From Figure 3.5(a) and (b), we know that increasing A_d or declining k_d can effectively increase $I_h(t)$. Especially, I_h will decrease and tend to zero if $A_d = 6 \times 10^5$ or $k_d = 0.4$. The effect of transmission rate β_{dd} between dogs (or β_{cc} between CFBs) on I_h is shown in Figure 3.5(c), where we can see that reducing the transmission rate between dogs is more effective to control rabies than that between CFBs. Figure 3.5(d) shows that reducing the transmission rate β_{dh} (from dogs to humans) is more important to control rabies than that of β_{ch} (from CFBs to humans).

The initial conditions adopted in model fitting are mostly assumed. So it is necessary to study the influence of initial conditions on the rabies epidemics which are showed in Figures 3.6 and 3.7. From Figures 3.6 and 3.7, it is clear that the influence of initial value $S_d(0)$ is stronger than that of other initial values. This indicates that decreasing the number of dogs is really an important method to control the rabies.

Finally, Figure 3.8 shows the influence of different initial value conditions of dogs on the infected CFBs rabies cases $I_c(t)$. Once again we can see that the initial value $S_d(0)$ has a stronger influence on $I_c(t)$ than other initial conditions. It implies that the increasing number of dogs is really an important factor for rabies infection in CFBs.

Notice that public education and awareness about rabies could help to reduce the transmission rates from dogs (β_{dh}) and CFBs (β_{ch}) to humans via reducing the contacts and decreasing the probabilities of infection and to increase the vaccination (postexposure prophylaxis) rate.

4 Discussion

Rabies virus is present among various mammal species, including red fox and raccoon dog in Europe; raccoon, red fox, skunk, and insectivorous bats in North America; domestic dogs, insectivorous and vampire bats in South America; and domestic dogs, bat, Chinese ferret badger, raccoon dog, rat, fox, and wolf in Asia (Wang et al. [39]). Since the pioneer work of Anderson et al. [4] modeling the transmission of rabies in fox populations in Europe, many mathematical

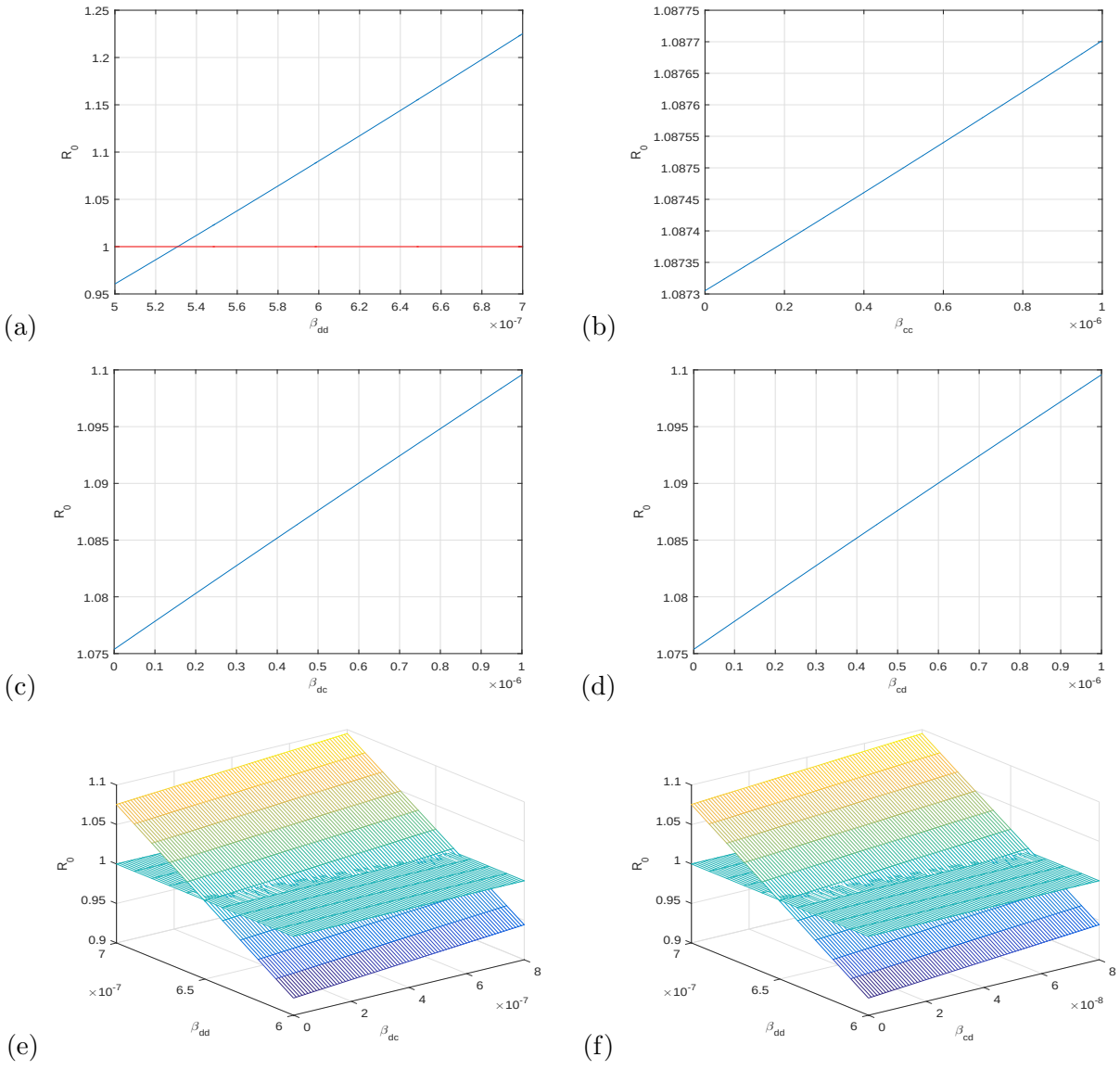


Figure 3.3: The graph of R_0 in terms of (a) dog-to-dog transmission rate β_{dd}; (b) CFB-to-CFB transmission rate β_{cc}; (c) dog-to-CFB transmission rate β_{dc}; (d) CFB-to-dog transmission rate β_{cd}; (e) β_{dd} and β_{dc}; (f) β_{dd} and β_{cd}.

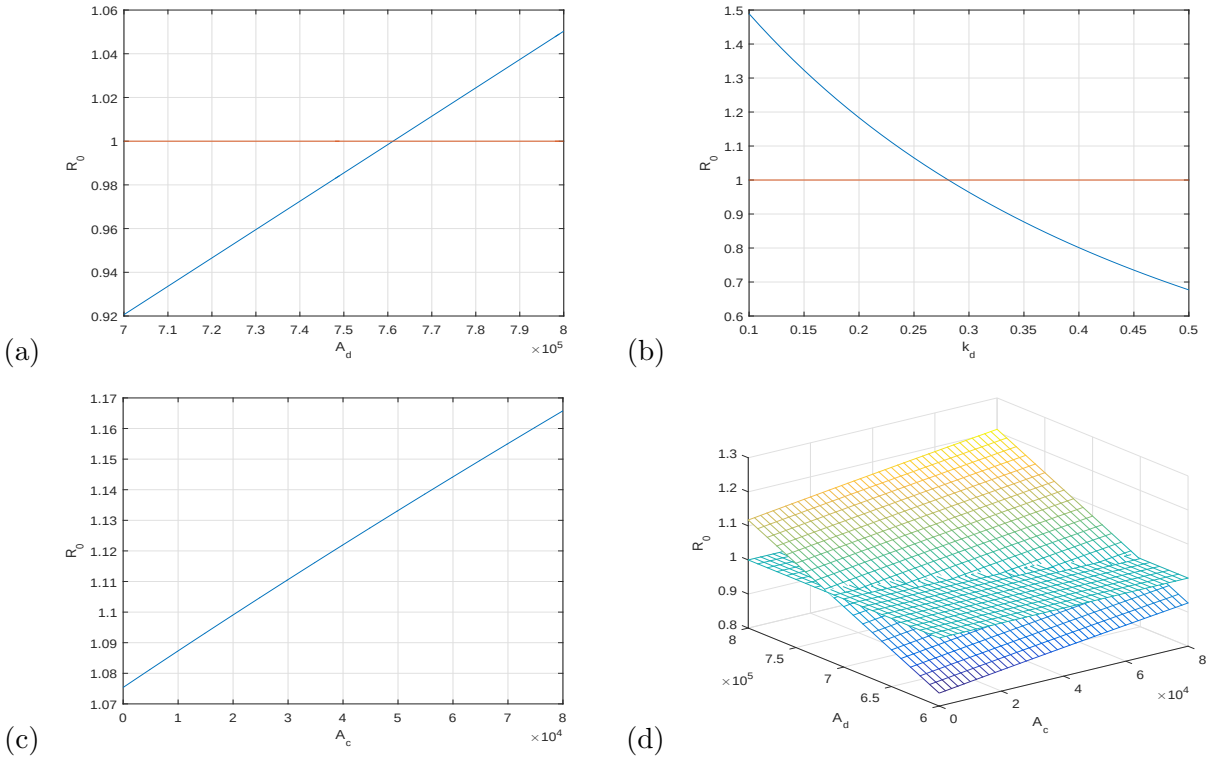


Figure 3.4: The influence of parameters on $R(0)$ (a) versus dog recruitment rate A_d; (b) versus dog vaccination rate k_d; (c) versus CFB recruitment rate A_c; (d) versus A_d and A_c.

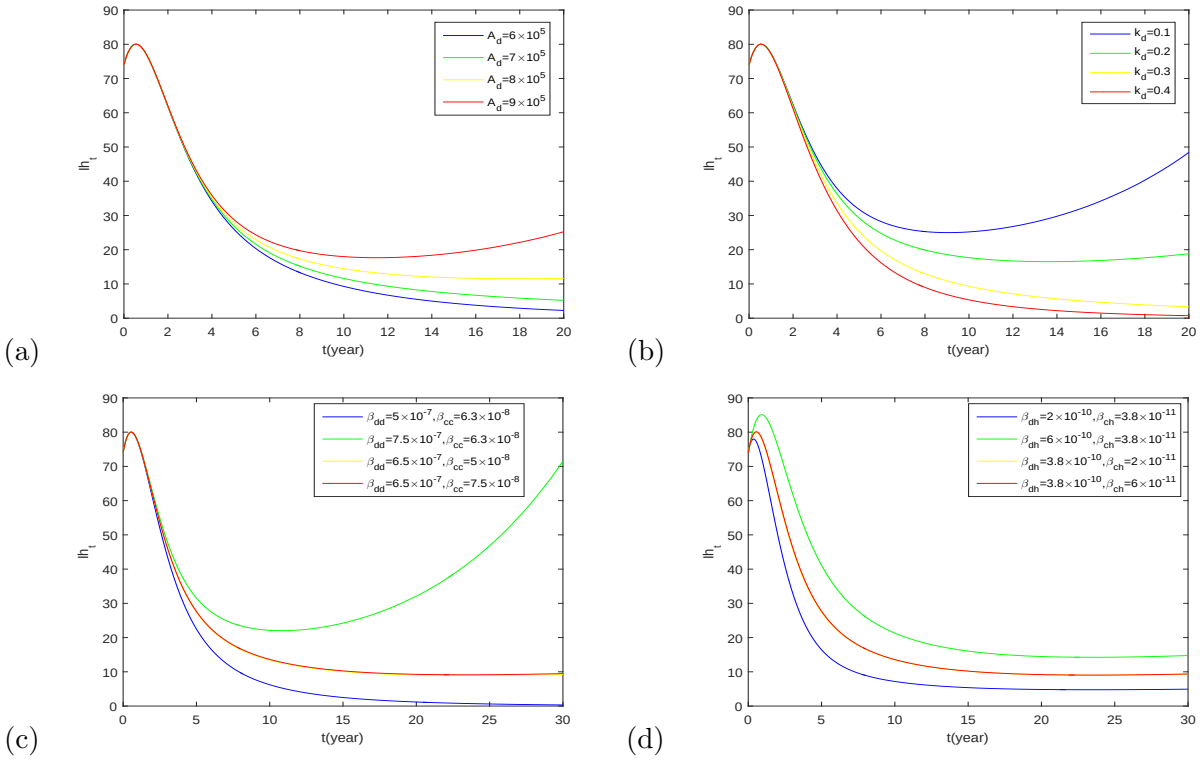


Figure 3.5: Simulations of infected human rabies cases I_h in Zhejiang Province (a) versus A_d; (b) versus k_d; (c) versus β_{cc} and β_{dd}; (d) versus β_{dh} and β_{ch}.

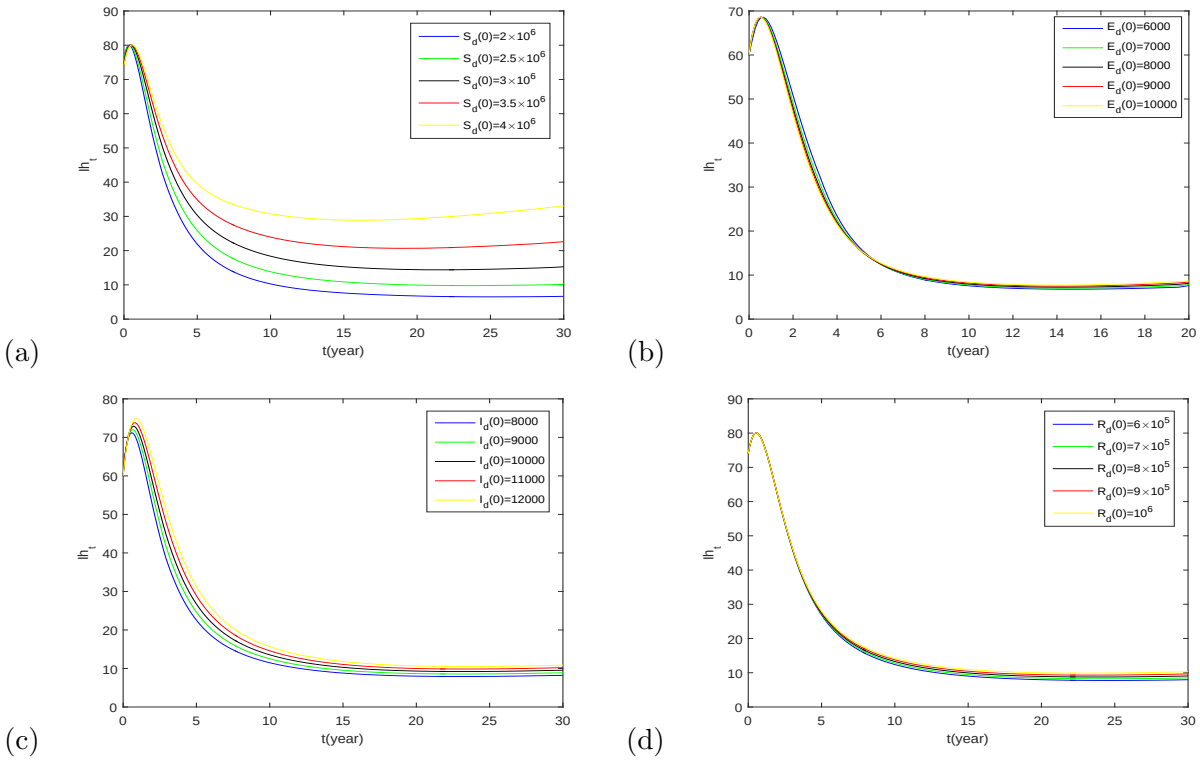


Figure 3.6: Simulations of infected human rabies cases I_h in Zhejiang Province with (a) different initial values of $S_d(0)$; (b) different initial values of $E_d(0)$; (c) different initial values of $I_d(0)$; and (d) different values of $R_d(0)$.

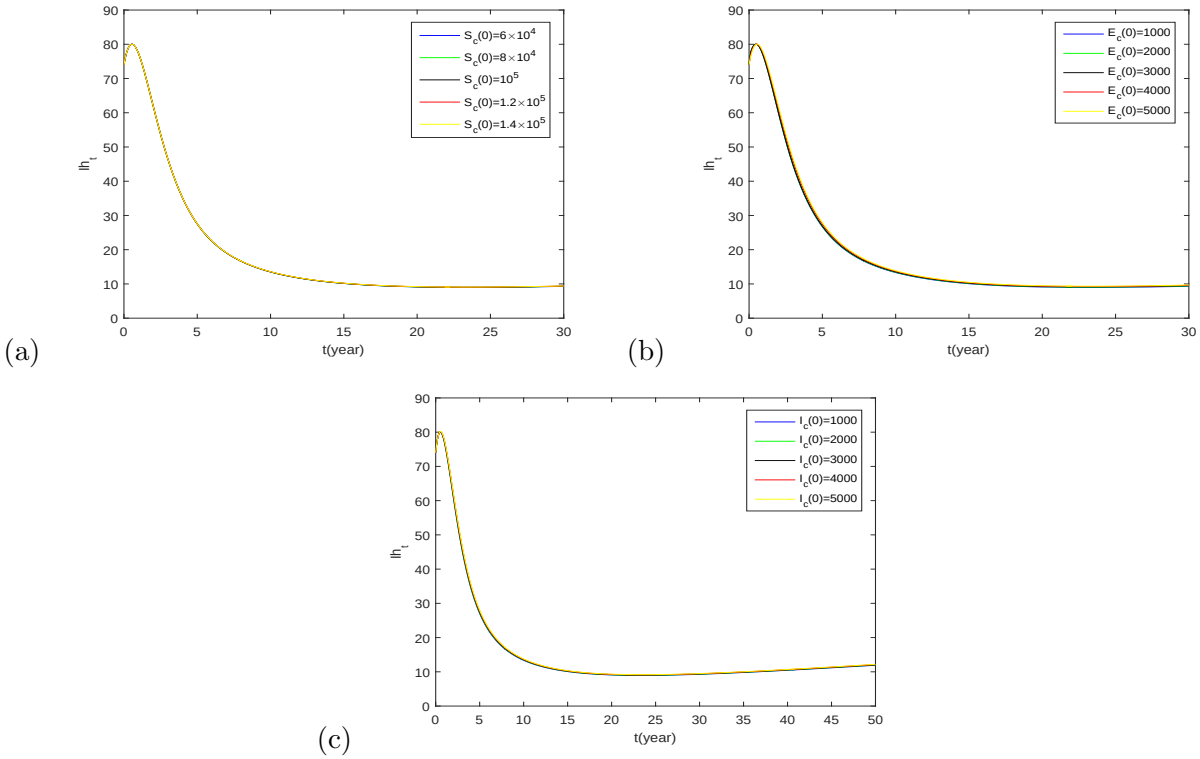


Figure 3.7: Simulations of infected human rabies cases I_h in Zhejiang Province with (a) different values of $S_c(0)$; (b) different values of $E_c(0)$; (c) different values of $I_c(0)$.

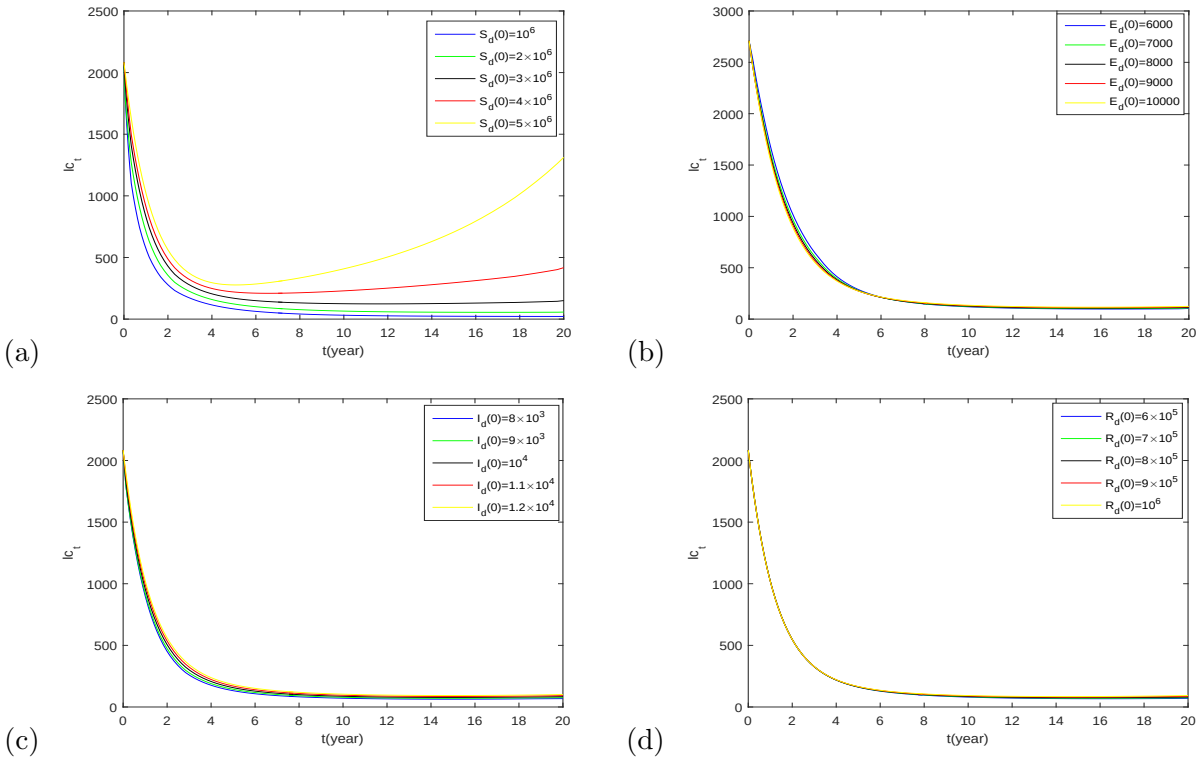


Figure 3.8: Simulations of infected CFB rabies cases I_c in Zhejiang Province with (a) different values of $S_d(0)$; (b) different values of $E_d(0)$; (c) different values of $I_d(0)$; (d) different values of $R_d(0)$.

models have been developed to study the transmission of rabies in different wild animals ([3, 5, 10, 13, 24, 35]). Recently, there have been some studies on modeling canine and human rabies in China ([45, 22, 46, 47, 9, 32]).

In this paper, taking into account the fact that human rabies in Zhejiang Province are casued by both infected dogs and CFBs, we proposed a multi-host zoonotic SEIR model for the dog-CFB-human transmission of rabies. The model describes the transmission of rabies among dogs and CFBs as well as the transmission from dogs and CFBs to humans. With estimated parameters, numerical simulation of the model agreed with the human rabies data reported by the Department of Health of Zhejiang Province and gave an estimate of the basic reproduction number $R_0 = 1.0114$. The sensitivity analysis of R_0 in terms of the model parameters demonstrated that rabies control and prevention strategies should include public education and awareness about rabies, increasing dog vaccination rate, reducing the dog and CFB interactions, and avoiding CFB bites or contact.

Since CFB-originated human rabies cases have been reported in Anhui, Jiangxi and Zhejiang Provinces (Wang et al. [39]), our model can be used to study the transmission dynamics of rabies among dogs, CFBs, and humans in these provinces as well and similar control measures can be designed. Also other wild animal originated, such as bat- and wolf-originated, human rabies have been reported in northeastern China (Jilin and Inner Mongolia), similar models can be developed. In order to control human rabies, national surveillance network need to be developed to collect data not only on dogs but also on wild animals. As wild animals move around, reaction-diffusion models might be more realistic to describe the spatial transmission of rabies (Ruan [33]).

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