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ORIGINAL ARTICLE

Modeling Seasonal Rabies Epidemics in China

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Abstract Human rabies, an infection of the nervous system, is a major public-health problem in China. In the last 60 years (1950–2010) there had been 124,255 reported human rabies cases, an average of 2,037 cases per year. However, the factors and mechanisms behind the persistence and prevalence of human rabies have not become well understood. The monthly data of human rabies cases reported by the Chinese Ministry of Health exhibits a periodic pattern on an annual base. The cases in the summer and autumn are significantly higher than in the spring and winter. Based on this observation, we propose a susceptible, exposed, infectious, and recovered (SEIRS) model with periodic transmission rates to investigate the seasonal rabies epidemics. We evaluate the basic reproduction number R_0, analyze the dynamical behavior of the model, and use the model to simulate the monthly data of human rabies cases reported by the Chinese Ministry of Health. We also carry out some sensitivity analysis of the basic reproduction number R_0 in terms of various model parameters. Moreover, we demonstrate that it is more reasonable to regard R_0 rather than the average basic reproduction number $\bar{R}_0$ or the basic reproduction number $\hat{R}_0$ of the corresponding autonomous system as a threshold for the disease. Finally, our studies show that human rabies in China can be controlled by reducing the birth rate of dogs, increasing the immunization rate of dogs, enhancing public education and awareness about rabies, and strengthening supervision of pupils and children in the summer and autumn.

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1 Introduction

Rabies, a fatal disease of humans and many other mammals, is caused by a virus which is associated with the bite and virus-containing saliva of an infected host (CDC 2010a). Rabies may affect all mammals, including livestock and pets. In most African and Asian countries dogs continue to be the main hosts and are responsible for most of the human rabies deaths (WHO 2010a).

Infective dogs can bite other dogs and humans and spread the rabies virus. After entering the body, the rabies virus travels quickly along the neural pathways to the noncentral nervous system, from there the virus further spreads to other organs and causes morbidity by intruding many tissues. Infected individuals can experience incubation before showing symptoms. The incubation period of the disease is usually a few months, but can be as long as years, depending on the distance the virus must travel to reach the central nervous system. If the bitten location is near the head, the incubation is relatively shorter. The first symptoms of rabies may be very similar to those of the flu expressing fever or headache, progressing to symptoms of cerebral dysfunction, anxiety, confusion, fearing light and water within days. With the disease exacerbating, the infected individual may experience delirium, abnormal behavior, hallucinations, and insomnia (CDC 2010b). Once the rabies virus reaches the central nervous system and symptoms of the disease develop, the course of the disease is less than 10 days (CDC 2010b) and the mortality rate reaches up to 100%.

Rabies transmission in dogs can be prevented by vaccination. Treatment of humans after exposure, known as post-exposure prophylaxis (PEP), is highly successful in preventing the disease if administered promptly. Although it is a vaccine-preventable disease, rabies still remains a neglected, untreatable public-health problem in many countries in Asia and Africa where 95% of human deaths occur (WHO 2010b).

Recently, mathematical models have been used to study the rabies epidemics in dogs and the transmission dynamics of rabies from dogs to humans. For example, Hampson et al. (2007) observed rabies epidemics cycles with a period of 3–6 years in dog populations in Africa and built a susceptible, exposed, infectious, and vaccinated model with an intervention response variable to show significant synchrony. Zinsstag et al. (2009) classified both dog and human populations in susceptible, exposed, infectious, and immunized classes and proposed a model for dog–human transmission dynamics and economics of rabies control in an African city.

Human rabies is a major public-health problem in China. Since 1950, human rabies has been classified as a class II infectious disease in the National Stationary Notifiable Communicable Diseases and the annual data of human rabies have been archived by the Chinese Center for Disease Control and Prevention. In the last 60 years (1950–2010) there had been 124,255 human rabies cases reported by the Chinese Ministry of Health (MOHC 2009, 2011), an average of 2,037 cases per year.

However, the factors and mechanisms behind the persistence and prevalence of human rabies have not been well understood. Most recently, Zhang et al. (2011) developed a deterministic model to study the transmission dynamics of rabies in China. The model, consisted of susceptible, exposed, infectious, and recovered subpopulations of both dogs and humans and described by eight ordinary differential equations, was used to simulate the human rabies data from 1996 to 2010 reported by the Chinese Ministry of Health. It was shown that reducing dog birth rate and increasing dog immunization coverage rate are the most effective methods for controlling rabies in China and large scale culling of susceptible dogs can be replaced by immunization of them. Hou et al. (2012) proposed a similar dog–human interaction model considering both domestic and wild dogs and used the model to simulate the rabies data from Guangdong Province, China. It was shown that the quantity of stray dogs also plays an important role in the transmission of rabies.

After the outbreaks of Severe Acute Respiratory Syndromes (SARS) in 2003, the Chinese Ministry of Health started to publish reported cases about the National Stationary Notifiable Communicable Diseases every month. We observe that the monthly data of human rabies cases reported by the Chinese Ministry of Health since January 2004 exhibit a periodic pattern on an annual base. The cases in the summer and autumn are significantly higher than in the spring and winter (MOHC 2009, 2011). Song et al. (2009) also reported that the main seasons for rabies epidemics in China are summer and fall. Moreover, the infected areas are mainly distributed in the south provinces such as Sichuan, Hunan, Guangxi, Guangdong, Anhui, Fujian (Song et al. 2009), which demonstrates that rabies transmission depends on the weather.

It is well-known that many diseases exhibit seasonal fluctuations, such as whooping cough, measles, influenza, polio, chickenpox, mumps, etc. (Bjornstad et al. 2002; Dowell 2001; London and Yorke 1973). Seasonally effective contact rate (Dushoff et al. 2004; Schwartz 1992; Schwartz and Smith 1983; Smith 1983), periodic changing in the birth rate (Ma and Ma 2006) and vaccination program (Earn et al. 2000) are often regarded as sources of periodicity. In this paper, we take periodic transmission rate into account based on the following facts. (1) In the summer and fall, people wear light clothing and are lack of protection for the bites or scratches of dogs. Also, in summer and fall people, in particular farmers, have more frequent outdoor activities which increase the chance of human–dog interaction. (2) In these seasons, dogs are more maniacal and apt to attack each other and humans. (3) From July to September schools are closed for summer vacations and children are out of supervision and enjoy tantalizing dogs. In fact, it was reported (Song et al. 2009) that 25.7% of human rabies cases in China are students and unattended children. (4) In addition, temperature may be related to the fluctuation of diseases. Under high temperature in summer, rabies virus can survive easily and its infectivity is stronger.

The purpose of this paper is to propose a susceptible, exposed, infectious, and recovered (SEIRS) model with periodic transmission rates to investigate the seasonal rabies epidemics. We will evaluate the basic reproduction number R_0, analyze the dynamical behavior of the model, and use the model to simulate the monthly data of human rabies cases reported by the Chinese Ministry of Health from January 2004. We will also carry out some sensitivity analysis of the basic reproduction number R_0 in terms of various model parameters. Moreover, we will show that it is more reasonable to regard R_0 rather than the average basic reproduction number $\bar{R}_0$ or the basic

reproduction number $\hat{R}_0$ of the corresponding autonomous system as a threshold for the disease. Finally, we will explore some effective control measures for the rabies epidemics in China.

The article is organized as follows. In Sect. 2, we introduce the model and present the expression of the basic reproduction number. Then we study the global asymptotic stability of the disease-free equilibrium and the existence of positive periodic solutions. Simulations of the model and sensitivity analysis of the basic reproduction number are performed in Sect. 3. In Sect. 4, we give a brief discussion. The detailed calculation of the basic reproduction number using the spectral radius of the operator is presented in the Appendix.

2 Mathematical Modeling and Analysis

2.1 Model Formulation

We denote the total numbers of dogs and humans by $N(t)$ and $N_1(t)$, respectively, and classify each of them into four subclasses: susceptible, exposed, infectious and recovered, with the numbers of dogs denoted by $S(t)$, $E(t)$, $I(t)$, and $R(t)$, and human sizes denoted by $S_1(t)$, $E_1(t)$, $I_1(t)$, and $R_1(t)$, respectively. The transmission dynamics associated with these subpopulations are illustrated in Fig. 1.

The transmission rate between $S(t)$ and $I(t)$ is $\beta(t)$, the transmission rate between $S_1(t)$ and $I(t)$ is $\beta_1(t)$, and humans do not spread rabies to each other. We can write transmission rate $\beta(t)$ in the general form $\beta(t) = \lambda_0\beta'(N)\beta''/N$, where N is the total number of dogs, $\beta'(N)$ is the number of dogs that a susceptible dog comes across per unit time, β'' is the probability of getting bitten after interacting with the susceptible dog, and λ_0 is the probability of being infected after bitten for the susceptible dog. We can express $\beta_1(t)$ similarly. As discussed in the Introduction, in the summer and fall there are more frequent interactions among dogs and between dogs and humans and these coefficients are more likely to change as season changes. Thus we use the periodic functions $\beta(t) = a[1 + b\sin(\frac{\pi}{6}t + 5.5)]$ and $\beta_1(t) = a_1[1 + b_1\sin(\frac{\pi}{6}t + 5.5)]$ proposed by Schenzle (1984) to describe the transmission rates among dogs and from dogs to humans, where a and a_1 are the baseline contact rates and b and b_1 are the magnitudes of forcing.

The birth numbers of dogs and humans per unit time are constant. Vaccination is often applied to seemingly healthy dogs ($S(t)$ and $E(t)$) and people bitten by dogs ($E_1(t)$). Particularly, we need to interpret that k_1 and k are the products of the vaccination coverage rate and the vaccination effective rate. However, there is a protection period for rabies vaccine. Thus, we import loss rates of immunity λ and λ_1. Because not all the exposeds will develop clinical outbreak, clinical outcome rates γ and γ_1 are presented. Natural death rates are m and m_1, and disease-related death rates are μ and μ_1, respectively.

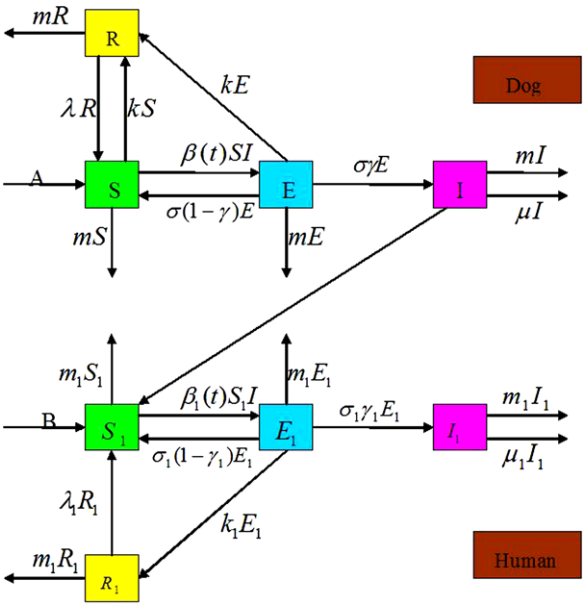

Fig. 1 The transmission diagram of rabies among dogs and from dogs to humans

The model is a system of ordinary differential equations:

$$\begin{cases} \frac{dS}{dt} = A + \lambda R + \sigma(1-\gamma)E - mS - \beta(t)SI - kS, \\ \frac{dE}{dt} = \beta(t)SI - mE - \sigma(1-\gamma)E - kE - \sigma\gamma E, \\ \frac{dI}{dt} = \sigma\gamma E - mI - \mu I, \\ \frac{dR}{dt} = k(S+E) - mR - \lambda R, \\ \frac{dS_1}{dt} = B + \lambda_1 R_1 + \sigma_1(1-\gamma_1)E_1 - m_1 S_1 - \beta_1(t)S_1 I, \\ \frac{dE_1}{dt} = \beta_1(t)S_1 I - m_1 E_1 - \sigma_1(1-\gamma_1)E_1 - k_1 E_1 - \sigma_1\gamma_1 E_1, \\ \frac{dI_1}{dt} = \sigma_1\gamma_1 E_1 - m_1 I_1 - \mu_1 I_1, \\ \frac{dR_1}{dt} = k_1 E_1 - m_1 R_1 - \lambda_1 R_1, \end{cases} \tag{1}$$

where all parameters are positive, the interpretations and values of parameters are described in Table 1, $\beta(t) = a[1 + b\sin(\frac{\pi}{6}t + 5.5)]$ and $\beta_1(t) = a_1[1 + b_1\sin(\frac{\pi}{6}t + 5.5)]$.

2.2 Global Stability of the Disease-Free Equilibrium

Notice that from the equations in model (1), we have

$$\begin{cases} \frac{dN}{dt} = A - mN - \mu I, \\ \frac{dN_1}{dt} = B - m_1 N_1 - \mu_1 I_1. \end{cases} \tag{2}$$

Let $X = \{(S, E, I, R, S_1, E_1, I_1, R_1) | S, E, I, R, S_1, E_1, I_1, R_1 \geq 0, 0 < S + E + I + R \leq \frac{A}{m}, 0 < S_1 + E_1 + I_1 + R_1 \leq \frac{B}{m_1}\}$.

Table 1 Descriptions and values of parameters in model (1)

Para.	Value	Unit	Interpretation	Source
A	2.34×10^5	month^{-1}	Dog birth population	Estimation
λ	$\frac{1}{6}$	month^{-1}	Dog loss rate of immunity	Assumption
i	1.045	month	Dog incubation period	Zinsstag et al. (2009)
σ	$\frac{1}{1.045}$	month^{-1}	$1/i$	Zinsstag et al. (2009)
γ	0.49	month^{-1}	Clinical outcome rate of exposed dogs	Zinsstag et al. (2009)
m	0.0064	month^{-1}	Dog natural mortality rate	Assumption
a	9.9×10^{-8}	none	The baseline contact rate	Estimation
b	0.41	none	The magnitude of forcing	Estimation
k	0.09	month^{-1}	Dog vaccination rate	MOHC (2009)
μ	1	month^{-1}	Dog disease-related death rate	MOHC (2009)
B	1.34×10^6	month^{-1}	Human birth population	NBSC (2009)
λ_1	$\frac{1}{6}$	month^{-1}	Human loss rate of immunity	ChinaCDC (2011)
i_1	2	month	Human incubation period	ChinaCDC (2011)
σ_1	$\frac{1}{2}$	month^{-1}	$1/i_1$	ChinaCDC (2011)
γ_1	0.5	month^{-1}	Clinical outcome rate of exposed humans	AnshanCDC (2011)
m_1	0.00057	month^{-1}	Human natural mortality rate	NBSC (2009)
a_1	2.41×10^{-11}	none	The baseline contact rate	Estimation
b_1	0.23	none	The magnitude of forcing	Estimation
k_1	0.54	month^{-1}	Human vaccination rate	MOHC (2009)
μ_1	1	month^{-1}	Human disease-related death rate	MOHC (2009)

Theorem 2.1 *The region X is positively invariant with respect to system* (1).

It is easy to see that system (1) has one disease-free equilibrium

$$P_0 = (\hat{S}, 0, 0, \hat{R}, \hat{S}_1, 0, 0, 0),$$

where

$$\hat{S} = \frac{(m+\lambda)A}{m(m+\lambda+k)}, \qquad \hat{R} = \frac{kA}{m(m+\lambda+k)}, \qquad \hat{S}_1 = \frac{B}{m_1}.$$

We can evaluate the basic reproduction number R_0 for system (1) following the definition of Bacaer and Guernaoui (2006) and the general calculation procedure in Wang and Zhao (2008), which is defined as z_0 such that $g(z_0) = 1$, where

$$g(z) = \frac{1}{2}\left\{\sqrt{\frac{(\mu-\sigma-k)^2 - 4(\lambda_2(T)+m+\mu)(\lambda_1(T)+m+\mu)}{[\lambda_1(T)-\lambda_2(T)]^2}\left[e^{\int_0^T \lambda_2(t)\,dt} - e^{\int_0^T \lambda_1(t)\,dt}\right]^2}\right\} + \frac{1}{2}\left[e^{\int_0^T \lambda_2(t)\,dt} + e^{\int_0^T \lambda_1(t)\,dt}\right].$$

The detailed computations are given in the Appendix.

Before analyzing the disease-free equilibrium, we make a claim.

Lemma 2.2 *For an arbitrary positive number θ, there is $t_2 > 0$ such that for all $t > t_2$, $S \le \hat{S} + \theta$.*

Proof From the last equation of system (1), we have

$$\begin{aligned}\frac{dR}{dt} &= k(S+E) - mR - \lambda R \\ &= k(N - R - I) - mR - \lambda R \\ &\le k\frac{A}{m} - (k + m + \lambda)R.\end{aligned}$$

Thus, for a positive number $\theta_1 = \frac{(m+k)\theta}{\lambda}$, there is $t_1 > 0$ such that for all $t > t_1$, $R(t) \le \frac{kA}{m(m+\lambda+k)} + \theta_1 = \hat{R} + \theta_1$. Also from the first two equations of system (1), we have for all $t > t_1$

$$\begin{aligned}\frac{d(S+E)}{dt} &= A + \lambda R - m(S+E) - k(S+E) - \sigma\gamma E \\ &\le A + \lambda(\hat{R} + \theta_1) - (m+k)(S+E),\end{aligned}$$

which implies that

$$\lim_{t\to\infty} \sup(S+E) \le \frac{A + \lambda(\hat{R} + \theta_1)}{m+k}.$$

Because $E \ge 0$, it follows that

$$\begin{aligned}\lim_{t\to\infty} \sup S &\le \frac{A + \lambda(\hat{R} + \theta_1)}{m+k} \\ &= \frac{A + \lambda(\frac{A}{m} - \hat{S} + \theta_1)}{m+k} \\ &= \hat{S} + \frac{\lambda\theta_1}{m+k}.\end{aligned}$$

Thus, there is $t_2 > 0$ such that for all $t > t_2 > t_1$, $S(t) \le \hat{S} + \theta$, where $\theta = \frac{\lambda\theta_1}{m+k}$. □

Theorem 2.3 *The disease-free equilibrium P_0 is globally asymptotically stable when $R_0 < 1$.*

Proof If $R_0 < 1$, we know that $\rho(\Phi_{F-V}(\omega)) < 1$ by Theorem 2.2 in Wang and Zhao (2008). We can choose $\theta > 0$ small enough such that $\rho(\Phi_{F-V+M_\theta}(\omega)) < 1$, where

$$M_\theta = \begin{pmatrix} 0 & 0 & \theta & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Considering the region X and using Lemma 2.2, we know that $S_1(t) \le \hat{S}_1 = \frac{B}{m_1}$ and $S(t) \le \hat{S} + \theta, t > t_2 > t_1$. Thus, when $t > t_2 > t_1$, we derive

$$\begin{cases} \frac{dE}{dt} \le \beta(t)(\hat{S} + \theta)I - (m + \sigma + k)E, \\ \frac{dE_1}{dt} \le \beta_1(t)\hat{S}_1 I - (m_1 + \sigma_1 + k_1)E_1, \\ \frac{dI}{dt} = \sigma\gamma E - mI - \mu I, \\ \frac{dI_1}{dt} = \sigma_1\gamma_1 E_1 - m_1 I_1 - \mu_1 I_1. \end{cases} \tag{3}$$

Consider the following comparison system:

$$\begin{cases} \frac{dE}{dt} = \beta(t)(\hat{S} + \theta)I - (m + \sigma + k)E, \\ \frac{dE_1}{dt} = \beta_1(t)\hat{S}_1 I - (m_1 + \sigma_1 + k_1)E_1, \\ \frac{dI}{dt} = \sigma\gamma E - mI - \mu I, \\ \frac{dI_1}{dt} = \sigma_1\gamma_1 E_1 - m_1 I_1 - \mu_1 I_1, \end{cases} \tag{4}$$

that is,

$$\frac{dh}{dt} = \big(F(t) - V(t) + M_\theta\big)h(t), \quad h(t) = \big(E(t), E_1(t), I(t), I_1(t)\big). \tag{5}$$

By Lemma 2.1 in Zhang and Zhao (2007), it follows that there exists a positive ω-periodic function $\hat{h}(t)$ such that $h(t) = e^{pt}\hat{h}(t)$ is a solution of system (4), where $p = \frac{1}{\omega}\ln\rho(\Phi_{F-V+M_\theta}(\omega))$. We know when $R_0 < 1$, $\rho(\Phi_{F-V+M_\theta}(\omega)) < 1$. Therefore, we have $h(t) \to 0$ as $t \to \infty$, which implies that the zero solution of system (4) is globally asymptotically stable. Applying the comparison principle (Smith and Waltman 1995), we know that for system (1), $E(t) \to 0$, $I(t) \to 0$, $E_1(t) \to 0$ and $I_1(t) \to 0$ as $t \to \infty$. By the theory of asymptotic autonomous systems (Thieme 1992), it is also known that $S(t) \to \hat{S}$, $R(t) \to \hat{R}$, $S_1(t) \to \hat{S}_1$ and $R_1(t) \to 0$ as $t \to \infty$. So P_0 is globally attractive when $R_0 < 1$. It follows that P_0 is globally asymptotically stable when $R_0 < 1$. □

2.3 Existence of Positive Periodic Solutions

Define

$$X_0 := \big\{(S, E, I, R, S_1, E_1, I_1, R_1) \in X : E > 0, I > 0, E_1 > 0, I_1 > 0\big\}$$

and $\partial X_0 = X \setminus X_0$. Denote $u(t, x_0)$ as the unique solution of system (1) with the initial value $x_0 = (S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0)$. Let $P : X \to X$ be the Poincaré map associated with system (1), i.e.,

$$P(x_0) = u(\omega, x_0), \quad \forall x_0 \in X,$$

where ω is the period. Applying the fundamental existence–uniqueness theorem (Perko 2000), we know that $u(t, x_0)$ is the unique solution of system (1) with $u(0, x_0) = x_0$. From Theorem 2.1, we know that X is positively invariant and P is point dissipative.

Lemma 2.4 *When $R_0 > 1$, then there exists a $\delta > 0$ such that when*

$$\left\|\left(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0\right) - P_0\right\| \le \delta$$

for any $(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0) \in X_0$, we have

$$\limsup_{m\to\infty} d\left[P^m\left(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0\right), P_0\right] \ge \delta,$$

where $P_0 = (\hat{S}, 0, 0, \hat{R}, \hat{S}_1, 0, 0, 0)$.

Proof If $R_0 > 1$, we obtain $\rho(\Phi_{F-V}(\omega)) > 1$ by Theorem 2.2 in Wang and Zhao (2008). Choose $\epsilon > 0$ small enough such that $\rho(\Phi_{F-V-M_\epsilon}(\omega)) > 1$, where

$$M_\epsilon = \begin{pmatrix} 0 & 0 & \epsilon & 0 \\ 0 & 0 & \epsilon & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Now we proceed by contradiction to prove that

$$\limsup_{m\to\infty} d\left(P^m\left(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0\right), P_0\right) \ge \delta.$$

If not, then

$$\limsup_{m\to\infty} d\left(P^m\left(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0\right), P_0\right) < \delta$$

for some $(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0) \in X_0$. Without loss of generality, we assume that $d(P^m(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0), P_0) < \delta$ for all $m \ge 0$. By the continuity of the solutions with respect to the initial values, we obtain

$$\left\|u\left(t, P^m\left(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0\right)\right) - u(t, P_0)\right\| \le \epsilon, \quad \forall m \ge 0,\ \forall t_1 \in [0, \omega].$$

For any $t \ge 0$, let $t = m\omega + t_1$, where $t_1 \in [0, \omega]$ and $m = [\frac{t}{\omega}]$, which is the greatest integer less than or equal to $\frac{t}{\omega}$. Then we have

$$\begin{aligned} &\left\|u\left(t, \left(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0\right)\right) - u(t, P_0)\right\| \\ &\quad = \left\|u\left(t_1, P^m\left(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0\right)\right) - u(t_1, P_0)\right\| \le \epsilon \end{aligned}$$

for any $t \ge 0$, which implies that $\hat{S} - \epsilon \le S(t) \le \hat{S} + \epsilon$, $\hat{S}_1 - \epsilon \le S_1(t) \le \hat{S}_1 + \epsilon$, $t \ge 0$. Then for $\|(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0) - P_0\| \le \delta$, we have

$$\begin{cases} \frac{dE}{dt} \ge \beta(t)(\hat{S} - \epsilon)I - (m + \sigma + k)E, \\ \frac{dE_1}{dt} \ge \beta_1(t)(\hat{S}_1 - \epsilon)I - (m_1 + \sigma_1 + k_1)E_1, \\ \frac{dI}{dt} = \sigma\gamma E - mI - \mu I, \\ \frac{dI_1}{dt} = \sigma_1\gamma_1 E_1 - m_1 I_1 - \mu_1 I_1. \end{cases} \tag{6}$$

Next we consider the linear system

$$\begin{cases} \frac{dE}{dt} = \beta(t)(\hat{S} - \epsilon)I - (m + \sigma + k)E, \\ \frac{dE_1}{dt} = \beta_1(t)(\hat{S}_1 - \epsilon)I - (m_1 + \sigma_1 + k_1)E_1, \\ \frac{dI}{dt} = \sigma\gamma E - mI - \mu I, \\ \frac{dI_1}{dt} = \sigma_1\gamma_1 E_1 - m_1 I_1 - \mu_1 I_1. \end{cases} \tag{7}$$

Once again by Lemma 2.1 in Zhang and Zhao (2007), it follows that there exists a positive ω-periodic function $\hat{g}(t)$ such that $g(t) = e^{pt}\hat{g}(t)$ is a solution of system (7), where $p = \frac{1}{\omega}\ln\rho(\Phi_{F-V-M\epsilon}(\omega))$. Because $\rho(\Phi_{F-V-M\epsilon}(\omega)) > 1$, when $g(0) > 0$, $g(t) \to \infty$ as $t \to \infty$. Applying the comparison principle (Smith and Waltman 1995), we know that when $E(0) > 0$, $I(0) > 0$, $E_1(0) > 0$ and $I_1(0) > 0$, $E(t) \to \infty$, $I(t) \to \infty$, $E_1(t) \to \infty$ and $I_1(t) \to \infty$ as $t \to \infty$. This is a contradiction. The proof of the lemma is complete. □

Theorem 2.5 *System* (1) *has at least one positive periodic solution.*

Proof We first prove that $\{P^m\}_{m\geq 0}$ is uniformly persistent with respect to $(X_0, \partial X_0)$. First of all, we explain that X_0 and ∂X_0 are positively invariant. In fact, for any $(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0) \in X_0$, solving the equations of system (1), we derive that

$$\begin{aligned} S(t) &= e^{-\int_0^t (m+\beta(t)+k)\,dt}\left[S^0 + \int_0^t \big(A + \lambda R(t) + \sigma(1-r)E(t)\big)e^{\int_0^t (m+\beta(t)+k)\,dt}\,dt\right] \\ &\geq Ae^{-\int_0^t (m+\beta(t)+k)\,dt}\int_0^t e^{\int_0^t (m+\beta(t)+k)\,dt} \\ &> 0, \quad \forall t > 0, \end{aligned} \tag{8}$$

$$\begin{aligned} R(t) &= e^{-(m+\lambda)t}\left[R^0 + \int_0^t k\big(S(t) + E(t)\big)e^{(m+\lambda)t}\,dt\right] \\ &\geq e^{-(m+\lambda)t}\int_0^t kS(t)e^{(m+\lambda)t}\,dt \\ &> 0, \quad \forall t > 0, \end{aligned} \tag{9}$$

$$\begin{aligned} E(t) &= e^{-(m+\sigma+k)t}\left[E^0 + \int_0^t \beta(t)S(t)I(t)e^{(m+\sigma+k)t}\,dt\right] \\ &\geq e^{-(m+\sigma+k)t}\int_0^t \beta(t)S(t)I(t)e^{(m+\sigma+k)t}\,dt \\ &> 0, \quad \forall t > 0, \end{aligned} \tag{10}$$

and

$$\begin{aligned} I(t) &= e^{-(m+\mu)t}\left[I^0 + \int_0^t \sigma\gamma E(t)e^{(m+\mu)t}\,dt\right] \\ &\geq e^{-(m+\mu)t}\int_0^t \sigma\gamma E(t)e^{(m+\mu)t}\,dt \\ &> 0, \quad \forall t > 0. \end{aligned} \tag{11}$$

Similarly, $S_1(t) > 0$, $R_1(t) > 0$, $E_1(t) > 0$ and $I_1(t) > 0$. So, X_0 is positively invariant. Clearly, ∂X_0 is relatively closed in X. Set

$$\begin{aligned} M_\partial = \big\{&\big(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0\big) \in \partial X_0 : \\ &P^m\big(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0\big) \in \partial X_0,\ \forall m \geq 0\big\}. \end{aligned}$$

It is easy to show that

$$M_\partial = \big\{(S, 0, 0, R, S_1, 0, 0, 0) \in X : S \geq 0, R \geq 0, S_1 \geq 0\big\}. \tag{12}$$

Note that

$$\big\{(S, 0, 0, R, S_1, 0, 0, 0) \in X : S \geq 0, R \geq 0, S_1 \geq 0\big\} \subseteq M_\partial,$$

we only need to prove that

$$M_\partial \subseteq \big\{(S, 0, 0, R, S_1, 0, 0, 0) \in X : S \geq 0, R \geq 0, S_1 \geq 0\big\}.$$

That is, for any $(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0) \in \partial X_0$, we have

$$E(m\omega) = I(m\omega) = E_1(m\omega) = I_1(m\omega) = 0, \quad \forall m \geq 0.$$

If there exists an $m_1 \geq 0$ such that

$$\big(E(m_1\omega), I(m_1\omega), E_1(m\omega), I_1(m\omega)\big)^T > 0,$$

by replacing the initial time 0 with $m_1\omega$ and following the processes as in (8)–(11), it can be seen that $S(t) > 0$, $R(t) > 0$, $S_1(t) > 0$, $R_1(t) > 0$. Analogously, we have $(E(t), I(t), E_1(t), I_1(t))^T > 0$, $\forall t > m_1\omega$. Thus, we have

$$\big(S(t), E(t), I(t), R(t), S_1(t), E_1(t), I_1(t), R_1(t)\big) \in X_0, \quad \forall t > m_1\omega,$$

which contradicts that $(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0) \in \partial X_0$ that requires

$$P^m\big(S^0, E^0, I^0, R^0, S_1^0, E_1^0, I_1^0, R_1^0\big) \in \partial X_0, \quad \forall m \geq 0.$$

So, the equality (12) holds, which implies that E_0 is the only fixed point of P and acyclic in ∂X_0.

Moreover, Lemma 2.4 implies that $P_0 = (\hat{S}, 0, 0, \hat{R}, \hat{S}_1, 0, 0, 0)$ is an isolated invariant set in X and $W^S(P_0) \cap X_0 = \emptyset$. By the acyclicity theorem on uniform persistence for maps (Theorem 1.3.1 and Remark 1.3.1 in Zhao 2003), it follows that P is uniformly persistent with respect to $(X_0, \partial X_0)$.

Now Theorem 1.3.6 in Zhao (2003) implies that P has a fixed point

$$\big(S^*(0), E^*(0), I^*(0), R^*(0), S_1^*(0), E_1^*(0), I_1^*(0), R_1^*(0)\big) \in X_0.$$

From the first equation of system (1) we have

$$\begin{aligned} S^*(t) &= e^{-\int_0^t (m+\beta(t)+k)\,dt}\left[S^*(0) + \int_0^t \big(A + \lambda R + \sigma(1-r)E\big)e^{\int_0^t (m+\beta(t)+k)\,dt}\,dt\right] \\ &\geq A e^{-\int_0^t (m+\beta(t)+k)\,dt} \int_0^t e^{\int_0^t (m+\beta(t)+k)\,dt} \\ &> 0, \quad \forall t \in [0, \omega]. \end{aligned}$$

The periodicity of $S^*(t)$ implies $S^*(t) > 0$ for all $t > 0$. Following the processes as in inequalities (8)–(11), we have $E^*(t) > 0$, $I^*(t) > 0$, $R^*(t) > 0$, $S_1^*(t) > 0$, $E_1^*(t) > 0$, $I_1^*(t) > 0$, $R_1^*(t) > 0$, for all $t \geq 0$. Therefore,

$$\big(S^*(t), E^*(t), I^*(t), R^*(t), S_1^*(t), E_1^*(t), I_1^*(t), R_1^*(t)\big)$$

is a positive ω-periodic solution of system (1). □

3 Simulations and Sensitivity Analysis

In this section, we first use model (1) to simulate the reported human rabies data of China from January 2004 to December 2010, predict the trend of the disease and seek for some control and prevention measures. The data, concerning human rabies from 2004 to 2010, are obtained mainly from epidemiologic bulletins published by the Chinese Ministry of Health (MOHC 2011). We need to estimate the parameters of model (1), most of which can be obtained from the literature or assumed on the basis of common sense. However, we have to estimate $\beta(t)$, $\beta_1(t)$ and A by using the least-square fitting of $I_1(t_i)$ through discretizing the ordinary differential system (1) as follows:

$$I_1(t_i + \Delta t) = \big(\sigma_1 r_1 E_1(t_i) - m_1 I_1(t_i) - \mu_1 I_1(t_i)\big)\Delta t + I_1(t_i). \tag{13}$$

The least-square fitting is to minimize the objective function

$$J(\theta) = \frac{1}{n}\sum_{i=1}^{n}\big(I(t_i) - \hat{I}(t_i)\big)^2, \tag{14}$$

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

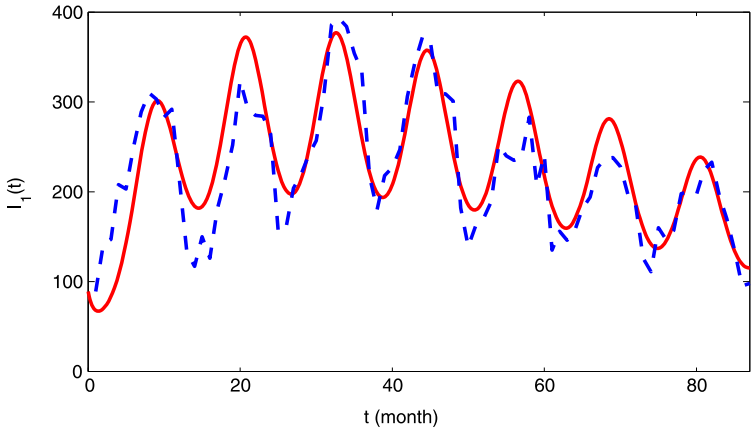

Fig. 2 The comparison between the reported human rabies data in mainland China from January 2004 to December 2010 and the simulation of our model. *The dashed curve* represents the monthly data reported by Ministry of Health of China while *the solid curve* is simulated by using our model. The values of parameters are given in Table 1. The initial values used in the simulations were $S(0) = 3.3 \times 10^7$, $E(0) = 2.2 \times 10^4$, $I(0) = 1.1 \times 10^4$, $R(0) = 3.3 \times 10^6$, $S_1(0) = 1.29 \times 10^9$, $E_1(0) = 178$, $I_1(0) = 89$, and $R_1(0) = 6 \times 10^7$

The values of parameters are listed in Table 1. We obtain the annual number of human population using the annual birth and death data from the National Bureau of Statistics of China (NBSC 2009). Then we calculate the average and divide it by 12 to derive the monthly human birth population $B = 1{,}340{,}000$. We need the initial values to perform the numerical simulations of the model. The number of the initial susceptible human population at the end of 2003, $S_1(0)$, is obtained from the China Statistical Yearbook and the number of the initial infective humans $I_1(0)$ is from epidemiological bulletins published by the Chinese Ministry of Health. However, the numbers of the initial exposed humans $E_1(0)$ and the recovered humans $R_1(0)$ cannot be obtained. We derive $E_1(0)$ reversely by the parameter γ and $R_1(0)$ is estimated roughly. Regarding the initial values for dogs, we only know that there are about 75 millions dogs in 2009 from online news. So, $S(0)$, $E(0)$, $I(0)$, and $R(0)$ are calculated reversely by the corresponding parameters r_1, k_1 and data fitting. The numerical simulation of the model on the number of human rabies cases is shown in Fig. 2. We observe that the data of 2005, 2008 and 2009 are slightly different from the solution as observed in Zhang et al. (2011). We think this is because of large scale culling of dogs in these years. However, culling of dogs is not considered in model (1).

Moreover, with these parameter values, we can roughly estimate that the basic reproduction number $R_0 = 1.03$ under the current circumstances in China. From Fig. 3, we can see that when $R_0 < 1$, the number of infected humans $I_1(t)$ tends to 0. On the contrary, when $R_0 > 1$, $I_1(t)$ tends to a stable periodic solution.

We can also predict the general tendency of the epidemic in a long term according to the current situation, which is presented in Fig. 4. From these figures we can see that the epidemic of rabies can be relieved in a short time, but cannot be eradicated with the current prevention and control measures.

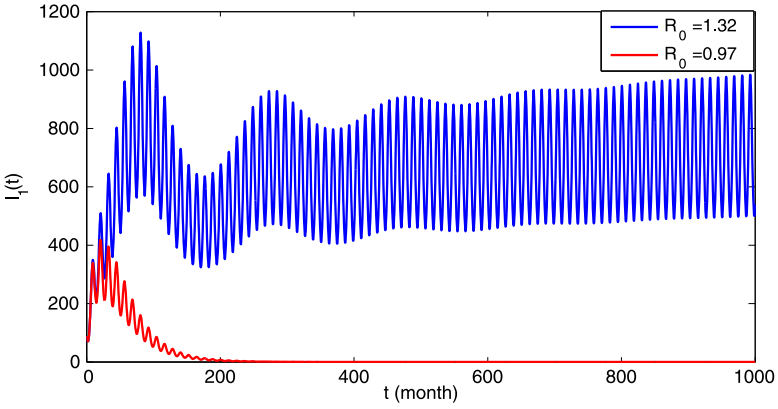

Fig. 3 The tendency of the human rabies infectious cases $I_1(t)$ in a long time with different values of R_0. When $A = 220{,}000$ (*lower curve*) and $300{,}000$ (*upper curve*), and the values of other parameters in Table 1 do not change, $R_0 = 0.97$ and 1.32, respectively

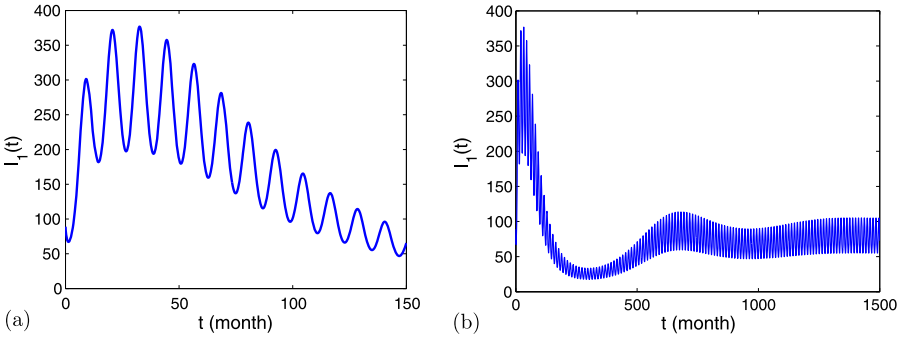

Fig. 4 The tendency of the human rabies infectious cases $I_1(t)$ in short and long times

The initial conditions adopted in model fitting are mostly assumed and back-extrapolated by parameters. So it is necessary to study the influence of initial conditions on the rabies epidemics which are showed in Figs. 5 and 6.

From Figs. 5 and 6, we can see that the initial value $S(0)$ has a stronger influence on $I_1(t)$ and other initial conditions have little or almost no effect on $I_1(t)$. It implies that the increasing number of dogs is really an important factor for the prevalence and persistence of rabies in China.

Finally, we perform some sensitivity analysis to determine the influence of parameters A, k, γ and a on R_0. From Fig. 7(a), it is obvious that when A is less than 226,920, R_0 can be less than 1. However, the annual birth population of dogs can achieve 400,000 or more in China. This indicates that human rabies in China cannot be eradicated if the birth number of dogs cannot be controlled under 2 million.

Post-exposure prophylaxis (PEP) is used for most situations for human rabies. In model (1), it is embodied in the terms k and k_1 and it can affect γ and γ_1. We observe that R_0 is a concave function of k from Fig. 7(b). So k has an obvious effect on R_0.

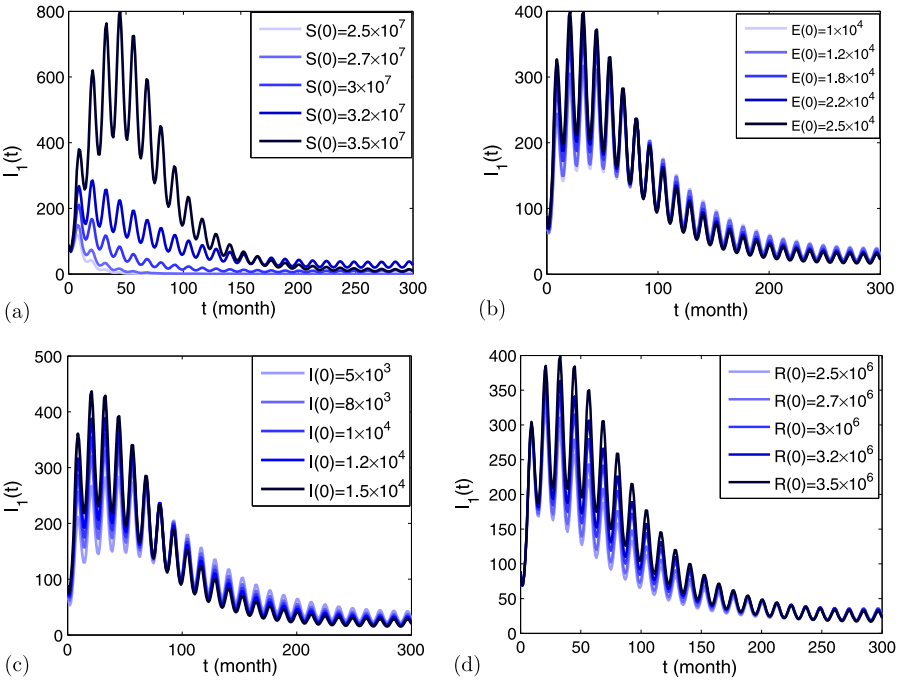

Fig. 5 The influence of initial conditions of dogs on the number of human rabies cases $I_1(t)$. (**a**) Different values of $S(0)$; (**b**) different values of $E(0)$; (**c**) different values of $I(0)$; (**d**) different values of $R(0)$

We also know that immunization is an effective measure to control rabies. Next, we consider the effect of γ on R_0, which is depicted in Fig. 7(c). We can observe that it is linear in γ. Most people, especially in the rural and remote areas, have little knowledge about rabies and even do not know what to do after being bitten by dogs. Song et al. (2009) reported that 66.3% of rabies victims did not seek medical services at all and 27.6% of the cases received inadequate PEP. Although the effect of γ on R_0 is less than k, we can enhance people the awareness and knowledge about rabies and the emergency measure and treatment after they are bitten and scratched by dogs to decrease the rate of clinical outbreak of rabies.

Now we discuss how a effects R_0 in Fig. 7(d). Although they are linear, a is very small and a slight change of a can lead to large variations of R_0. Since $\beta(t) = a[1 + b\sin(\frac{\pi}{6}t + 5.5)] = \lambda_0\beta'(N)\beta''/N$, we can manage a by controlling $\beta'(N)$, i.e., the number of dogs a susceptible dog runs into per unit time, which is to strengthen the management of dogs, especially stray dogs, in case they run wild and bite each other and humans.

Finally, we consider the combined influence of A and k, and a and k on R_0 in Fig. 8, respectively. From the contour surfaces, we can see that when vaccination, management of dogs and controlling the birth rate of dogs are combined, controlling rabies will be more effective. Moreover, the effect of a is greater than A by comparing the two figures.

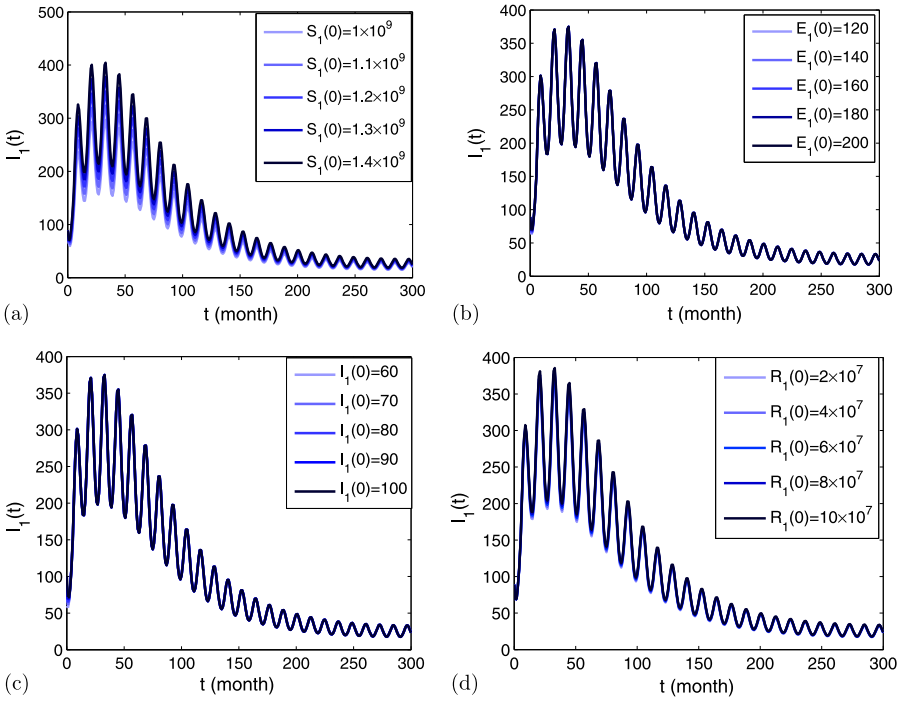

Fig. 6 The influence of initial conditions of humans on the number of human rabies cases $I_1(t)$. (**a**) Different values of $S_1(0)$; (**b**) different values of $E_1(0)$; (**c**) different values of $I_1(0)$; (**d**) different values of $R_1(0)$

In conclusion, controlling the population of dogs, reducing the birth rate of dogs, increasing the immunization rate of dogs, improve the management of dogs, enhancing the awareness of people about rabies, and combining these measures are effective measures to control rabies in China. In addition, because the monthly data of human rabies cases exhibits a periodic pattern on an annual base and the human rabies cases in the summer and autumn are higher, it will be useful to take extra measures from May to July every year before the infection peaks, such as extra supervision of children and students out of school.

4 Discussion

The transmission of rabies has been a growing concern in China. The data of human rabies cases reported by the Chinese Ministry of Health exhibit seasonal characteristics that the morbidity rates in the summer and autumn are much higher than in the winter and spring. In order to study the transmission dynamics of rabies in China, seasonality of the spreading of the rabies was incorporated into an SEIRS mathematic model with periodic transmission rates. Firstly, we calculated the basic reproduction number R_0 (Diekmann et al. 1990) and analyzed the dynamics of the model including the global stability of the disease-free equilibrium and the existence

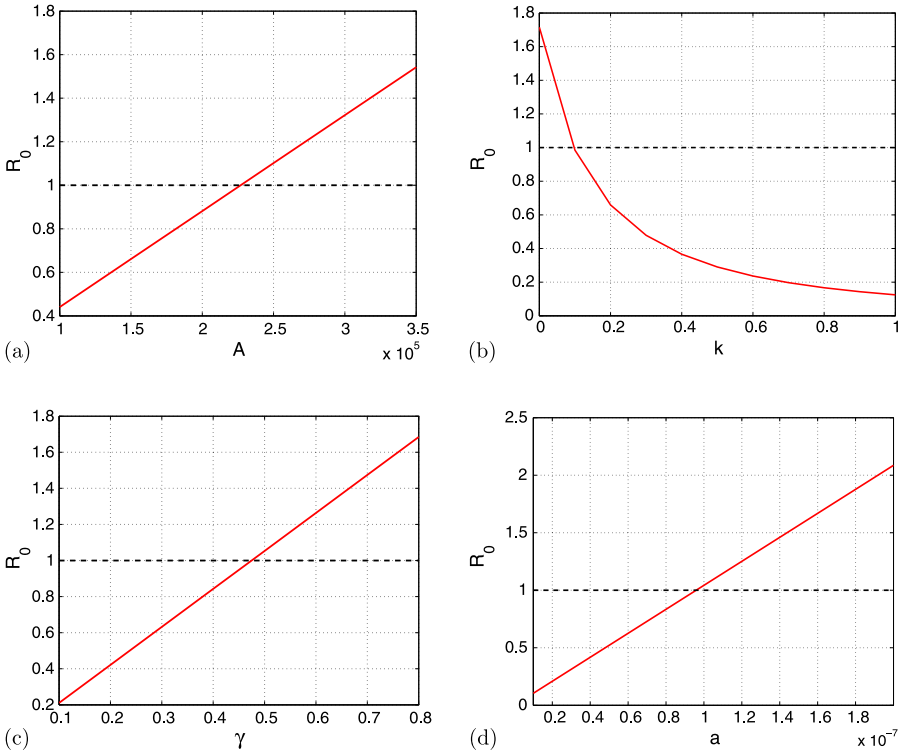

Fig. 7 The influence of parameters on R_0. (**a**) Versus A; (**b**) versus k; (**c**) versus γ; (**d**) versus a. Other parameter values in Table 1 do not change

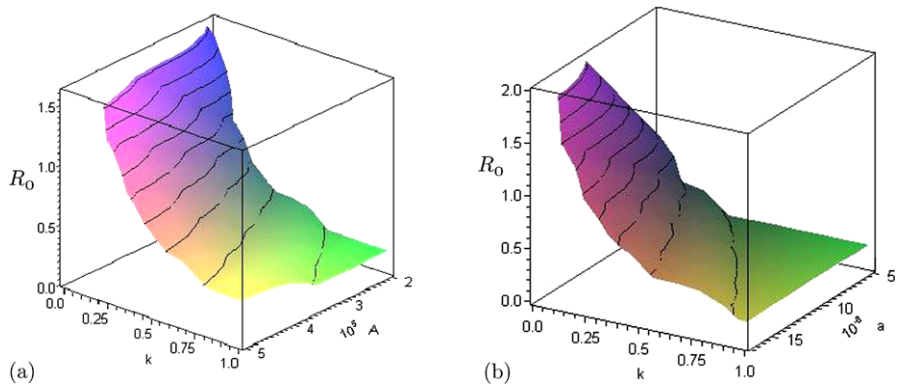

Fig. 8 The graph of R_0 in terms of (**a**) A and k and (**b**) a and k. Other parameter values in Table 1 do not change

of periodic solutions. R_0 was calculated following the definition of Bacaer and Guernaoui (2006), namely $R_0 = \rho(L)$, where L is the next infection operator, which has been employed in some other studies (Bai and Zhou 2011; Liu 2010; Liu et al. 2010;

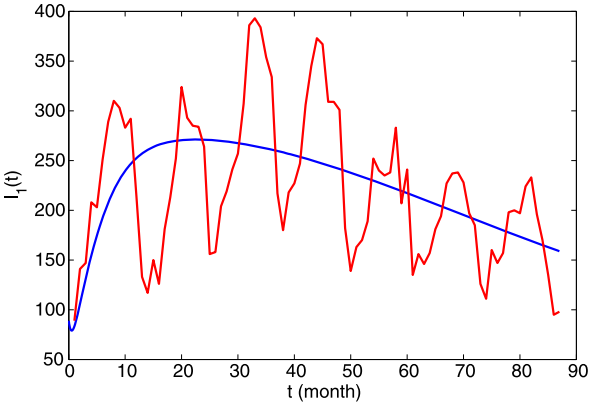

Fig. 9 The fitting result of the tendency of the infected human rabies cases $I_1(t)$ using the corresponding autonomous system. $A = 232{,}000$, $\beta = 9.56 \times 10^{-8}$, $\beta_1 = 3.68 \times 10^{-11}$ and other parameter values are the same as those in the nonautonomous system. *The oscillatory curve* is the data reported and *the skewed curve* is the fitting result by the autonomous system

Nakata and Kuniya 2010; Wang and Zhao 2008; Zhang and Zhao 2007). In particular, Wang and Zhao (2008) generalized the techniques and results of van den Driessche and Watmough (2002) to periodic ODE models and provided a recipe to calculate the basic reproduction number. Their results also indicate that R_0 is a threshold value for determining the local stability of the disease-free periodic solution. We then used our model to simulate the monthly data on the number of infected human cases from January 2004 to December 2010 in China reported by the Chinese Ministry of Health and predicted the general tendency of disease in China. Moreover, we carried out some sensitivity analysis of parameters on R_0. The demographic data were estimated from National Bureau of Statistics of China (NBSC 2009). The values of most parameters in our model were obtained from the literature or by assumptions. The values of $\beta(t)$, $\beta_1(t)$ and A were estimated through least-square fitting of $I_1(t_i)$ by discretizing the ordinary differential system as in Chowell et al. (2006) and Stafford et al. (2000).

Moreover, we discussed and compared the basic reproduction numbers under different conditions. In Sect. 3, we evaluated that $R_0 = 1.03$ for the nonautonomous model. We can also define and calculate the basic reproduction number for the corresponding autonomous system (see Diekmann et al. 2010; van den Driessche and Watmough 2002). In this case, the fitting results and parameter values which also are obtained by the least-square method are shown in Fig. 9. Comparing Fig. 9 with Fig. 2, we can see that the new model gives a better fit to the monthly human rabies cases.

The basic reproduction number of the corresponding autonomous system is

$$\hat{R}_0 = \frac{\sigma\gamma\beta\hat{S}}{(m+\sigma+k)(m+\mu)} = 1.$$

It can be seen that $\hat{R}_0$ is slightly less than R_0. From the fitting results and the basic reproduction number, we think that the nonautonomous system is better and biologically more realistic than our previous autonomous model (Zhang et al. 2011).

When studying the transmission dynamics of periodic epidemic models, some researchers use the average basic reproduction number $\bar{R}_0$, namely the basic reproduction number of the time-averaged autonomous system of the periodic epidemic

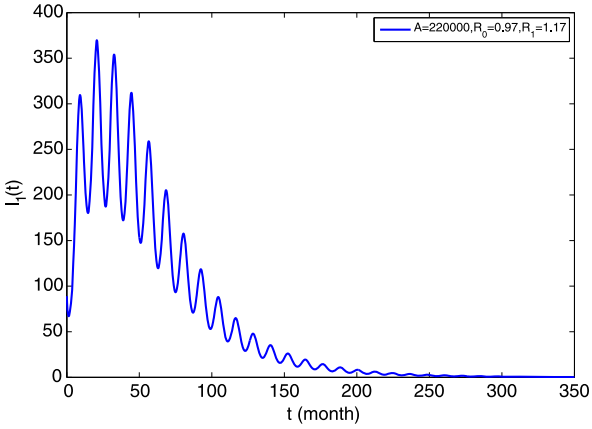

Fig. 10 The tendency of the human rabies infectious cases $I_1(t)$ when $A = 220{,}000$ and the values of other parameters do not change. Here, $R_0 = 0.97$ and $\bar{R}_0 = 1.17$

model over a time (Greenhalgh and Moneim 2003; Ma and Ma 2006; Moneim 2007; Wesley and Allen 2009; Williams 1997). However, the average basic reproduction number $\bar{R}_0$ can overestimate or underestimate infection risks. Using the expression of $\hat{R}_0$, we can give the corresponding average basic reproduction number in the nonautonomous system,

$$\bar{R}_0 = \frac{\sigma\gamma\bar{\beta}\hat{S}}{(m+\sigma+k)(m+\mu)},$$

where

$$\bar{\beta} = \frac{1}{12}\int_0^{12} \beta(t)\,dt, \qquad \hat{S} = \frac{(m+\lambda)A}{m(m+\lambda+k)}.$$

Using the parameter values in Table 1, we have $\bar{R}_0 = 1.24$, which is larger than R_0. By numerical simulations of our model, we found that the average basic reproduction number $\bar{R}_0$ overestimates infection risks. When $A = 220{,}000$ and other parameters values do not change, $R_0 = 0.97$ and $\bar{R}_0 = 1.17$. Note that $\bar{R}_0 = 1.17$ predicts that the disease should be prevalent. However, the curve in Fig. 10 tends to zero.

Furthermore, we would like to point out that Zhang et al. (2011) estimated that the basic reproduction number $R_0 = 2$, but in this paper, we calculated it to be 1.03 with similar model structure. This can be explained as follows. In Zhang et al. (2011), the data adopted by model fitting were from 1996 to 2010. In this paper we only used the data from 2004 to 2010. From Fig. 11, we can see that the numbers of infected human cases increased dramatically from 159 cases in 1996 and were fierce from 1996 to 2004. After 2004, the spread of rabies began to slow down. Moreover, the data in 2005 and after 2007 decreased. So the fact that R_0 in this paper is less than in previous paper is reasonable. We also would like to calculate the basic reproduction number for the nonautonomous system from 1996 to 2010. However, we cannot obtain the monthly data before 2004 since only after the SARS outbreaks in 2003 the Chinese Ministry of Health began to publish monthly data on various infectious diseases.

In summary, firstly we have proposed a nonautonomous system with periodic transmission rates to study the transmission dynamics of rabies in China, which is

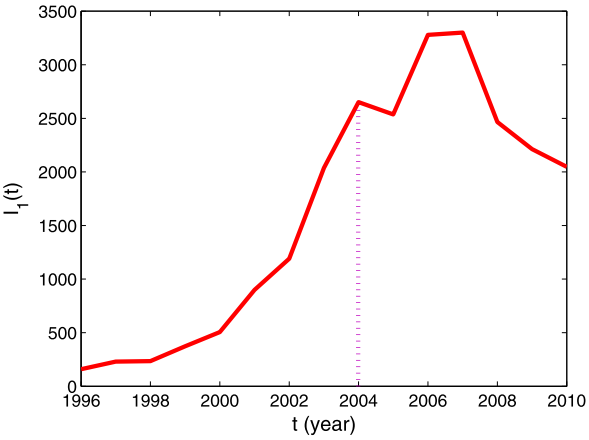

Fig. 11 The data of the number of human rabies cases from 1996 to 2010 reported by the Chinese Ministry of Health

more realistic and described the monthly rabies data from China more accurately. Moreover, the nonautonomous differential system is different from and better than the autonomous model used in Zhang et al. (2011). The dynamics, especially the basic reproduction number, are more complex. Thirdly, by comparing the basic reproduction numbers, we found that it is more realistic to regard R_0 rather than $\bar{R}_0$ or $\hat{R}_0$ as a threshold to determine whether the disease can establish or vanish eventually. Finally, we concluded that human rabies in China can be controlled by reducing the birth rate of dogs, increasing the immunization rate of dogs, enhancing the awareness of people about rabies, improving supervision of children and students in the summer, and increasing the medical service and treatment such as PEP after bitten by dogs.

Finally, we would like to comment that most human rabies cases in China are distributed the south provinces such as Guangdong, Guangxi, Guizhou, Hunan, Sichuan. However, the monthly data about human rabies cases we used in our simulations, reported by the Chinese Ministry of Health, were national data and homogeneous mixing was assumed in the model. In future studies, it will be very interesting to obtain regional rabies data (such as provincial data) and more realistic to make inhomogeneous mixing assumption. Reaction–diffusion equation models (Ruan and Wu 2009 and Zhang et al. 2012) or multi-patch models may be more suitable to study the spatial transmission dynamics of rabies in China. We leave these for future consideration.

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Appendix: Calculation of the Basic Reproduction Number

We evaluate the basic reproduction number R_0 for system (1) following the definition of Bacaer and Guernaoui (2006) and the general calculation procedure in Wang

and Zhao (2008). It is easy to see that system (1) has one disease-free equilibrium $P_0 = (\hat{S}, 0, 0, \hat{R}, \hat{S}_1, 0, 0, 0)$, where $\hat{S} = \frac{(m+\lambda)A}{m(m+\lambda+k)}$, $\hat{R} = \frac{kA}{m(m+\lambda+k)}$ and $\hat{S}_1 = \frac{B}{m_1}$. We rewrite the variables of system (1) as a vector $x = (E, E_1, I, I_1, S, S_1, R, R_1)$. Following Wang and Zhao (2008), we have

$$\mathcal{F} = \begin{pmatrix} \beta(t)SI \\ \beta_1(t)S_1I \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \qquad \mathcal{V} = \begin{pmatrix} mE + \sigma(1-\gamma)E + kE + \sigma\gamma E \\ m_1E_1 + \sigma_1(1-\gamma_1)E_1 + k_1E_1 + \sigma_1\gamma_1E_1 \\ mI + \mu I - \sigma\gamma E \\ m_1I_1 + \mu_1I_1 - \sigma_1\gamma_1E_1 \\ mS + \beta(t)SI + kS - [A + \lambda R + \sigma(1-\gamma)E] \\ m_1S_1 + \beta_1(t)S_1I - [B + \lambda_1R_1 + \sigma_1(1-\gamma_1)E_1] \\ mR + \lambda R - k(S+E) \\ m_1R_1 + \lambda_1R_1 - k_1E_1 \end{pmatrix},$$

$$\mathcal{V}^- = \begin{pmatrix} mE + \sigma(1-\gamma)E + kE + \sigma\gamma E \\ m_1E_1 + \sigma_1(1-\gamma_1)E_1 + k_1E_1 + \sigma_1\gamma_1E_1 \\ mI + \mu I \\ m_1I_1 + \mu_1I_1 \\ mS + \beta(t)SI + kS \\ m_1S_1 + \beta_1(t)S_1I \\ mR + \lambda R \\ m_1R_1 + \lambda_1R_1 \end{pmatrix},$$

$$\mathcal{V}^+ = \begin{pmatrix} 0 \\ 0 \\ \sigma\gamma E \\ \sigma_1\gamma_1E_1 \\ A + \lambda R + \sigma(1-\gamma)E \\ B + \lambda_1R_1 + \sigma_1(1-\gamma_1)E_1 \\ k(S+E) \\ k_1E_1 \end{pmatrix}.$$

So we derive

$$F(t) = \begin{pmatrix} 0 & 0 & \beta(t)\hat{S} & 0 \\ 0 & 0 & \beta_1(t)\hat{S}_1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V(t) = \begin{pmatrix} m+\sigma+k & 0 & 0 & 0 \\ 0 & m_1+\sigma_1+k_1 & 0 & 0 \\ -\sigma\gamma & 0 & m+\mu & 0 \\ 0 & -\sigma_1\gamma_1 & 0 & m_1+\mu_1 \end{pmatrix}.$$

We introduce some notation. Let $Y(t, s), t \geq s$, be the evolution operator of the system

$$\frac{dy}{dt} = -V(t)y. \tag{15}$$

That is, the 4×4 matrix $Y(t,s)$ satisfies

$$\frac{dY(t,s)}{dt} = -V(t)Y(t,s)$$

for any $t \geq s$, $Y(s,s) = I$, where I is the 4×4 identity matrix. Now we introduce the linear ω-periodic system

$$\frac{dw}{dt} = \left[-V(t) + \frac{F(t)}{z}\right]w, \quad t \in \mathbb{R}_+, \tag{16}$$

with parameter $z \in \mathbb{R}$. Let $W(t,s,z)$, $t \geq s$, be the evolution operator of system (16) on $\mathbb{R}^4$. Clearly, $\Phi_{F-V}(t) = W(t,0,1)$, $\forall t \geq 0$.

Following the method in Wang and Zhao (2008), we let $\phi(s)$ be ω-periodic in s and the initial distribution of infectious individuals. So $F(s)\phi(s)$ is the rate of new infections produced by the infected individuals who were introduced at time s. When $t \geq s$, $Y(t,s)F(s)\phi(s)$ gives the distribution of those infected individuals who were newly infected by $\phi(s)$ and remain in the infected compartments at time t. Naturally,

$$\int_{-\infty}^{t} Y(t,s)F(s)\phi(s)\,ds = \int_0^{\infty} Y(t,t-a)F(t-a)\phi(t-a)\,da$$

is the distribution of accumulative new infections at time t produced by all those infected individuals $\phi(s)$ introduced at time previous to t.

Let C_ω be the ordered Banach space of all ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^4$, which is equipped with the maximum norm $\|\cdot\|$ and the positive cone $C_\omega^+ := \{\phi \in C_\omega : \phi(t) \geq 0,\ \forall t \in \mathbb{R}_+\}$. Then we can define a linear operator $L : C_\omega \to C_\omega$ by

$$(L\phi)(t) = \int_0^{\infty} Y(t,t-a)F(t-a)\phi(t-a)\,da, \quad \forall t \in \mathbb{R}_+,\ \phi \in C_\omega.$$

L is called the next infection operator and the spectral radius of L is defined as the basic reproduction number

$$R_0 := \rho(L)$$

for the periodic epidemic model. To determine the threshold dynamics, we use Theorems 2.1 and 2.2 in Wang and Zhao (2008). First of all, we verify the seven assumptions in the theorems.

(1)–(5) The first five conditions can be verified by observing $\mathcal{F}$, $\mathcal{V}^+$ and $\mathcal{V}^-$.

(6) $\rho(\Phi_M(\omega)) < 1$, where $\rho(\Phi_M(\omega))$ is the spectral radius of $\Phi_M(\omega)$ and $\Phi_M(t)$ is the monodromy matrix of the linear ω-periodic system $\frac{dq}{dt} = M(t)q$ with

$$M = \begin{pmatrix} -m-k & 0 & \lambda & 0 \\ 0 & -m_1 & 0 & \lambda_1 \\ k & 0 & -(m+\lambda) & 0 \\ 0 & 0 & 0 & -(m_1+\lambda_1) \end{pmatrix}.$$

When M is a constant matrix, M is stable if and only if $\rho(\Phi_M(\omega)) < 1$. So, we just need to show that M is stable, that is, all eigenvalues are negative. It is

obvious that $-(m_1+\lambda_1)$ and $-m_1$ are the eigenvalues of M and are negative. Then we consider the eigenvalues of

$$\begin{pmatrix} -(m+k) & \lambda \\ k & -(m+\lambda) \end{pmatrix}.$$

By calculating, $-(m+k)-(m+\lambda)<0$ and $[-(m+k)]\times[-(m+\lambda)]-k\lambda = m^2+(k+\lambda)m>0$. So the remaining two eigenvalues are also negative. We can conclude that M is stable, namely $\rho(\Phi_M(\omega))<1$.

(7) $\rho(\Phi_{-V}(\omega))<1$, where $\Phi_{-V}(t)$ is the monodromy matrix of the linear ω-periodic system $\frac{dy}{dt}=-V(t)y$ with

$$-V=\begin{pmatrix} -m-\sigma-k & 0 & 0 & 0 \\ 0 & -m_1-\sigma_1-k_1 & 0 & 0 \\ \sigma\gamma & 0 & -m-\mu & 0 \\ 0 & -\sigma_1-\gamma_1 & 0 & -m_1+\mu_1. \end{pmatrix}.$$

Because $-V$ is a constant matrix, we need to show that $-V$ is stable. We can see that the eigenvalues of $-V$ are the diagonal elements and negative. So this condition is satisfied.

Using (ii) in Theorem 2.1 in Wang and Zhao (2008), we derive

$$\Phi_{F-\frac{V}{z}}(t)=W(\omega,0,z)=\begin{pmatrix} a_{11} & 0 & a_{13} & 0 \\ a_{21} & a_{22} & a_{23} & 0 \\ a_{31} & 0 & a_{33} & 0 \\ a_{41} & a_{42} & a_{43} & a_{44} \end{pmatrix},$$

where

$$\lambda_1(t)=\frac{-(2m+\sigma+k+\mu)+\sqrt{(\sigma+k-\mu)^2+\frac{4\beta(t)\hat{S}\sigma\gamma}{z}}}{2},$$

$$\lambda_2(t)=\frac{-(2m+\sigma+k+\mu)-\sqrt{(\sigma+k-\mu)^2+\frac{4\beta(t)\hat{S}\sigma\gamma}{z}}}{2},$$

$$a_{11}=\frac{\lambda_1(T)+m+\mu}{\lambda_1(T)-\lambda_2(T)}e^{\int_0^T\lambda_1(t)\,dt}-\frac{\lambda_2(T)+m+\mu}{\lambda_1(T)-\lambda_2(T)}e^{\int_0^T\lambda_2(t)\,dt},$$

$$a_{13}=\frac{[\lambda_1(T)+m+\mu][\lambda_2(T)+m+\mu]}{\sigma\gamma[\lambda_2(T)-\lambda_1(T)]}\left[e^{\int_0^T\lambda_1(t)\,dt}-e^{\int_0^T\lambda_2(t)\,dt}\right],$$

$$a_{21}=e^{-(m_1+\sigma_1+k_1)T}\int_0^T\frac{\beta_1(t)\hat{S}_1}{z}a_{31}e^{\int_0^t\lambda_1(t)\,dt}e^{(m_1+\sigma_1+k_1)t}\,dt,$$

$$a_{22}=e^{-(m_1+\sigma_1+k_1)T},$$

$$a_{23}=e^{-(m_1+\sigma_1+k_1)T}\int_0^T\frac{\beta_1(t)\hat{S}_1}{z}a_{33}e^{(m_1+\sigma_1+k_1)t}\,dt,$$

$$a_{31} = \frac{\sigma\gamma}{\lambda_1(T) - \lambda_2(T)}\left[e^{\int_0^T \lambda_1(t)\,dt} - e^{\int_0^T \lambda_2(t)\,dt}\right],$$

$$a_{33} = \frac{\lambda_2(T) + m + \mu}{\lambda_2(T) - \lambda_1(T)} e^{\int_0^T \lambda_1(t)\,dt} - \frac{\lambda_1(T) + m + \mu}{\lambda_2(T) - \lambda_1(T)} e^{\int_0^T \lambda_2(t)\,dt},$$

$$a_{41} = e^{-(m_1+\mu_1)T} \int_0^T \sigma_1\gamma_1 a_{21} e^{(m_1+\mu_1)t}\,dt,$$

$$a_{42} = \frac{\sigma_1\gamma_1}{\mu_1 - \sigma_1 - k_1} e^{-(m_1+\mu_1)T}\left[e^{(\mu_1-\sigma_1-k_1)T} - 1\right],$$

$$a_{43} = e^{-(m_1+\mu_1)T} \int_0^T \sigma_1\gamma_1 a_{23} e^{(m_1+\mu_1)t}\,dt,$$

$$a_{44} = e^{-(m_1+\mu_1)T}.$$

We see that all eigenvalues of the above matrix are real and the largest one is

$$g(z) = \frac{1}{2}\left\{\sqrt{\frac{(\mu - \sigma - k)^2 - 4(\lambda_2(T) + m + \mu)(\lambda_1(T) + m + \mu)}{[\lambda_1(T) - \lambda_2(T)]^2}\left[e^{\int_0^T \lambda_2(t)\,dt} - e^{\int_0^T \lambda_1(t)\,dt}\right]^2}\right\} + \frac{1}{2}\left[e^{\int_0^T \lambda_2(t)\,dt} + e^{\int_0^T \lambda_1(t)\,dt}\right].$$

So the basic reproduction number is z_0 such that $g(z_0) = 1$.

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