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Dynamics of rabies epidemics and the impact of control efforts in Guangdong Province, China

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ABSTRACT

Rabies is a major public health problem in some developing countries including China. One of the reasons is that there is a very large number of dogs, both domestic and stray, especially in Guangdong Province which has the third most rabies cases (after Guangxi and Hunan) among the 31 provinces, autonomous regions and municipalities in Mainland China, and at least 18.2% of the human rabies cases are caused by stray dogs. In this paper, based on the reported data and characteristics of the rabies infection in Guangdong Province, we propose a mathematical model for the dog–human transmission of rabies. We first determine the basic reproduction number R_0 and discuss the stability of the disease-free equilibrium and persistence of the disease. By carrying out sensitivity analysis of the basic reproduction number in terms of some parameters, we find that the domestic dog vaccination rate, the recruitment rate of domestic dogs, and the quantity of stray dogs play important roles in the transmission of rabies. This study suggests that rabies control and prevention strategies should include public education and awareness about rabies, increase of the domestic dog vaccination rate and reduction of the stray dog population.

1. Introduction

Rabies is a zoonotic viral disease maintained in domestic and wild carnivores and bats all over the world. It can be transmitted to other animals and humans through close contacts with saliva from infected animals. Once symptoms of the disease develop, its mortality rate is nearly 100%. Human rabies has been eradicated as a significant public health risk in most parts of the developed world and some developing countries in Latin America. However, approximately 55,000 deaths are reported annually world wide (Knobel et al., 2005), most of them from the developing world where the disease is a much greater problem, mainly because rabies is endemic in domestic dog populations (WHO, 1999). Despite the availability of mass vaccination and other effective tools for the control of rabies in domestic dog populations, the disease has been neglected in Asia and Africa where rabies incidence has been largely attributed to the population growth of domestic dogs (Knobel et al., 2005; Fooks, 2005).

Similar to the situation in many developing countries, rabies is a serious reemerging disease in China (Wu et al., 2009). Despite the high public health burden of more than 120,000 human deaths from rabies from 1950 to 2010, rabies is still neglected and not regarded as a priority in the disease control and prevention system in China (Hu et al., 2009). Most of the human rabies patients were infected by dog bites, accounting for 95% or more of the total cases (WHO, 2005). The number of dogs has increased gradually in China since the late 1990s. Now most households in Guangdong, Guangxi, Guizhou, and Hunan Provinces, where most of the rabies cases were recorded in recent years, have at least one dog. However, dog rabies surveillance often has not been carried out and most people are unaware of the risk of rabies in China. Domestic dog vaccination rate remains 2.8–6.4% (Hu et al., 2008), and only 30% or less of infected patients seek medical services or receive adequate post-exposure prophylaxis (PEP, which consists of local treatment of the wound, followed by vaccine therapy with or without rabies immunoglobulin) (Zhang et al., 2003; Si et al., 2008; Song et al., 2009). In Guangdong Province, there are more than three million domestic dogs and many stray dogs, but only about four hundred thousand rabies vaccines are sold every year. In particular, some infected domestic dogs are not treated properly and are abandoned by their hosts or run away from their hosts. From 2003 to 2004, 66.5% of the human rabies cases

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Table 1
Reported human rabies cases in Guangdong Province and China, 2006–2010.

Year	2006	2007	2008	2009	2010
Guangdong	387	334	319	330	301
China	3279	3300	2246	2213	2049
Percentage	11.8	10.2	14.2	14.9	14.7

were caused by domestic dogs and at least 18.2% by stray dogs and others (Si et al., 2008). Between 2006 and 2010, a total of 1671 human rabies cases were reported in Guangdong Province, the average outbreak rate is about 0.40/100,000, accounting for 12.7% of the total cases of China (DOHG, 2010; MOHC, 2010). See Table 1. After Guangxi and Hunan Provinces, Guangdong has the third most rabies cases in China (Si et al., 2008).

Various mathematical models have been developed to study the transmission dynamics of rabies, we refer to Artois et al. (1997), Smith and Cheeseman (2002), Bohrer et al. (2002), Murray and Seward (1992), Allen et al. (2002), Langlais and Suppo (2000), Harnos et al. (2006), Ding et al. (2007), Clayton et al. (2010), Tischendorf et al. (1998), Rhodes et al. (1998), and the references cited therein. However, most of their studies focused on the spread of rabies in wildlife animals such as fox and raccoon. Recently, some researchers proposed mathematical models for rabies epidemic in dogs and the transmission from dogs to humans. For example, Hampson et al. (2007) have studied synchronous cycles of domestic dog rabies in sub-Saharan Africa. Zinsstag et al. (2009) proposed a model for dog–human transmission dynamics and economics of rabies control in an African city. There are very few studies using mathematical models to study rabies epidemics in China (Zhang et al., 2011). In this paper, taking into account some specific characteristics of rabies transmission in Guangdong Province of China, we propose a susceptible–exposed–infectious–vaccinated (SEIV) model for the dog–human transmission of rabies taking both domestic and stray dogs into consideration. We first determine the basic reproduction number R_0 and analyze the stability and uniform persistence of the system, then we carry out some sensitivity analysis of R_0 on the segmental parameters and discuss the control of rabies infection in Guangdong Province of China.

The paper is organized as follows. In Section 2, we present the model and determine the basic reproduction number R_0. In Section 3, we analyze the stability of the disease-free equilibrium and uniform persistence of the model. Data simulations and sensitivity analysis of R_0 on various model parameters are carried out in Section 4. Various control measures and a brief discussion are given in Section 5.

2. Mathematical model and basic reproduction number

We classify each of the stray dog, domestic dog, and human populations into four subclasses: susceptible, exposed, infective and vaccinated. Let $S_0(t),E_0(t),I_0(t),V_0(t)$, and $S_1(t),E_1(t),I_1(t),V_1(t)$ denote the densities of susceptible, exposed, infective and vaccinated stray dog and domestic dog populations; $S_h(t),E_h(t)$, $I_h(t),V_h(t)$ denote the densities of susceptible, exposed, infective and vaccinated human populations at time t, respectively. The 12 compartments and model variables are given in Fig. 1.

There are some assumptions for the dog–human model: (i) the annual human birth population is constant; (ii) the infection of rabies virus is divided into three stages: prodromal, furious (or excitative) and paralytic. Once infected with rabies virus, dogs first experience the Symptoms of Prodromal stage, including lethargy, shyness and the desire to be alone, etc., lasting about two days, and then enter the furious stage (rabid domestic dogs leave their hosts to be stray dogs) (Shi, 2005), so we assume that the transmission rate from domestic dogs to stray dogs is zero; and (iii) the birth rate of stray dog is zero since newborn stray dogs are not taken care of by people and do not survive well in stray, and hence their survival rate is assumed to be almost zero. The mathematical model is governed by 12 ordinary differential equations.

Dogs:

$$
\begin{aligned}
\frac{dS_0}{dt} &= lS_1-(\mu+c)S_0-\beta_0 S_0 I_0+p_0E_0+\delta_1 V_0\\
\frac{dE_0}{dt} &= lE_1+\beta_0 S_0 I_0-(\mu+c+\sigma_0+p_0)E_0\\
\frac{dI_0}{dt} &= \sigma_0 E_0+\epsilon I_1-(\mu+c+\alpha)I_0\\
\frac{dV_0}{dt} &= lV_1-(\mu+c+\delta_1)V_0\\
\frac{dS_1}{dt} &= A-\beta S_1 I_0-\beta_1 S_1 I_1-(d+v+l)S_1+p_1E_1+\delta_2 V_1\\
\frac{dE_1}{dt} &= \beta S_1 I_0+\beta_1 S_1 I_1-(d+v+\sigma_1+l+p_1)E_1\\
\frac{dI_1}{dt} &= \sigma_1 E_1-(d+\epsilon+k)I_1\\
\frac{dV_1}{dt} &= v(S_1+E_1)-(d+l+\delta_2)V_1
\end{aligned}
\tag{1}
$$

Humans:

$$
\begin{aligned}
\frac{dS_h}{dt} &= H-\mu_h S_h-\lambda_{1h}S_h I_0-\lambda_{2h}S_h I_1+\delta_{1h}E_h+\delta_{2h}V_h\\
\frac{dE_h}{dt} &= \lambda_{1h}S_h I_0+\lambda_{2h}S_h I_1-(\mu_h+\sigma_h+\delta_{1h}+v_h)E_h\\
\frac{dI_h}{dt} &= \sigma_h E_h-(\mu_h+\alpha_h)I_h\\
\frac{dV_h}{dt} &= v_h E_h-(\mu_h+\delta_{2h})V_h
\end{aligned}
\tag{2}
$$

The parameters are described in Table 2. One can show that the region $X=\{(S_0,E_0,I_0,V_0,S_1,E_1,I_1,V_1):S_0,V_0,S_1,\quad V_1>0,E_0,I_0,\quad E_1,$ $I_1\geq 0;S_0+E_0+I_0+V_0+S_1+E_1+I_1+V_1\leq A/\min\{\mu+c,d\}\}$ is positively invariant for model (1). Therefore, $S_1+E_1+I_1+V_1\leq A/d+l$.

Now we derive the basic reproduction number of the model by the next generation matrix formulated in Diekmann et al. (1990) and van den Driessche and Watmough (2002). It is easy to see that model (1) always has a disease-free equilibrium $P_0=(S_0^0,0,0,$ $V_0^0,\ S_1^0,0,0,V_1^0)$, where

$$
S_0^0=\frac{Al(M_3M_7+\delta_1 v)}{(\mu+c)M_3(M_4M_7-\delta_2 v)},\quad S_1^0=\frac{AM_7}{M_4M_7-\delta_2 v}
$$

$$
V_0^0=\frac{Alv}{M_3(M_4M_7-\delta_2 v)},\quad V_1^0=\frac{Av}{M_4M_7-\delta_2 v}
$$

and

$$
\begin{aligned}
&M_1=\mu+c+\sigma_0+p_0,\quad M_2=\mu+c+\alpha,\quad M_3=\mu+c+\delta_1\\
&M_4=d+l+v,\quad M_5=d+v+l+\sigma_1+p_1,\quad M_6=d+k+\epsilon\\
&M_7=d+l+\delta_2
\end{aligned}
$$

We define the basic reproduction number by

$$
R_0=\frac{H+\sqrt{H^2-4G}}{2M_1M_2M_5M_6} \tag{3}
$$

where

$$
\begin{aligned}
H&=\sigma_0\beta_0M_5M_6S_0^0+\beta(\sigma_0 lM_6+\sigma_1\epsilon M_1)S_1^0+\sigma_1\beta_1M_1M_2S_1^0\\
G&=\sigma_0\sigma_1\beta_0\beta_1M_1M_2M_5M_6S_0^0S_1^0
\end{aligned}
$$

Note that

$$
H^2-4G\geq(\sigma_0\beta_0M_5M_6S_0^0-\sigma_1\beta_1M_1M_2S_1^0)^2\geq 0
$$

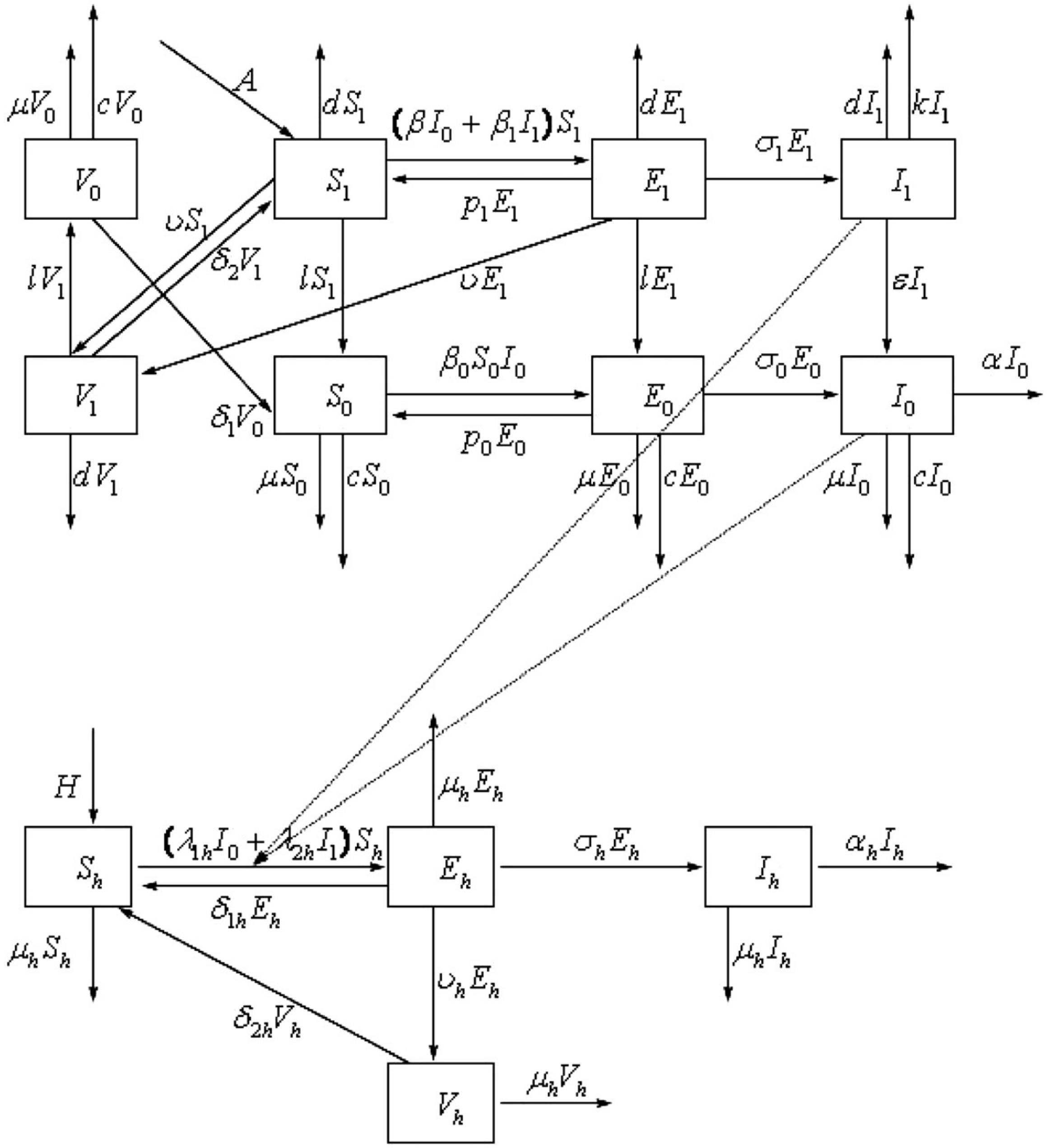

Fig. 1. Flowchart of rabies transmission between domestic and stray dogs and humans.

3. Extinction and uniform persistence of the disease

In this section, we investigate the global stability of disease-free equilibrium and uniform persistence of model (1).

Theorem 1. *If $R_0 < 1$, then the disease-free equilibrium P_0 of model* (1) *is globally asymptotically stable.*

Proof. From the equations of model (1), we have

$$\begin{aligned}\frac{dV_1}{dt} &= v(S_1+E_1)-dV_1-lV_1-\delta_2 V_1\\ &\le v\left(\frac{A}{d+l}-I_1-V_1\right)-dV_1-lV_1-\delta_2 V_1\\ &\le \frac{Av}{d+l}-vV_1-dV_1-lV_1-\delta_2 V_1\end{aligned}$$

and

$$\begin{aligned}\frac{d(S_1+E_1)}{dt} &= A+\delta_2 V_1-(d+l+v)(S_1+E_1)-\sigma_1 E_1\\ &\le A+\delta_2 V_1^0-(d+l+v)(S_1+E_1)\end{aligned}$$

Thus,

$$\limsup_{t\to\infty} V_1 = V_1^0, \quad \limsup_{t\to\infty}(S_1+E_1) = \frac{A+\delta_2 V_1^0}{d+l+v}$$

Because $E_1 \ge 0$, it follows that

$$\limsup_{t\to\infty} S_1 = \frac{A+\delta_2 V_1^0}{d+l+v} = S_1^0$$

From the first two equations of model (1), we have

$$\begin{aligned}\frac{d(S_0+E_0)}{dt} &= l(S_1+E_1)+\delta_1 V_0-(\mu+c)(E_0+S_0)-\sigma_0 E_0\\ &\le lS_1^0+\delta_1 V_0^0-(\mu+c)(E_0+S_0)\end{aligned}$$

Table 2
Parameters and their values (unit: year^{-1}).

Parameter	Value	Interpretation	Source
A	7.7×10^5	Domestic dog recruitment rate	Fitting
l	0.014	Rate of domestic dog abandoned	Fitting
μ	0.24	Stray dog mortality rate	Assumption
c	0.06	Stray dog culling rate	Assumption
δ_1	0.5	Stray dog loss of vaccination immunity rate	Assumption
δ_2	0.5	Domestic dog loss of vaccination immunity rate	Assumption
σ_0	0.35	Rate of clinical outcome of exposed stray dogs	[A]
σ_1	0.37	Rate of clinical outcome of exposed domestic dogs	[A]
p_0	0.35	Rate of no clinical outcome of exposed stray dogs	[A]
p_1	0.37	Rate of no clinical outcome of exposed domestic dogs	[A]
$\epsilon(>l)$	0.1	Transfer rate from rabid dogs to stray dogs	Fitting
α	1	Rabid dog mortality rate	MOHC (2009)
β_0	8×10^{-6}	Transmission rate from stray dogs to stray dogs	Fitting
β	4×10^{-6}	Transmission rate from stray dogs to domestic dogs	Fitting
β_1	3.2×10^{-7}	Transmission rate from domestic dogs to domestic dogs	Fitting
d	0.11	Domestic dog mortality rate	Assumption
v	0.133	Domestic dog vaccination rate	Si et al. (2007)
k	0.79	Domestic rabid dog culling rate	[B]
H	10^6	Annual human birth population	GSY (2010b)
μ_h	4.6×10^{-3}	Human mortality rate	GSY (2010a)
λ_{1h}	3.6×10^{-9}	Transmission rate from stray dogs to humans	Fitting
λ_{2h}	4.8×10^{-10}	Transmission rate from domestic dogs to humans	Fitting
δ_{1h}	0.33	Rate of no clinical outcome of exposed humans	[A]
δ_{2h}	1	Human loss of vaccination immunity rate	[B]
σ_h	0.33	Rate of clinical outcome of exposed humans	[A]
v_h	0.328	Human vaccination rate	Si et al. (2008)
α_h	1	Rabid human mortality rate	MOHC (2009)

Notes: [A] The rate of clinical outcome of the exposed dogs is about 30–70% (CCDC, 2006). Here, we estimate that it is 50%, so the probability of stray dog survival and clinical outbreak is $(1-0.24-0.06)\times0.5=0.35$. Similarly, the probability of domestic dog (human) survival and clinical outbreak is about 0.37 (0.33).
[B] $k=1-d-\epsilon$. In China, the valid time of rabies vaccination for humans is six months to one year, so we have $\delta_{2h}=1$.

Because $E_0\geq0$, it follows that

$$\lim_{t\to\infty}\sup S_0=\frac{lS_1^0+\delta_1V_0^0}{\mu+c}=S_0^0$$

Hence, we have proved that $S_0\leq S_0^0, S_1\leq S_1^0$.

From model (1), we also know that

$$\begin{cases}\dfrac{dE_0}{dt}\leq lE_1+\beta_0S_0^0I_0-\mu E_0-cE_0-\sigma_0E_0-p_0E_0\\ \dfrac{dI_0}{dt}=\sigma_0E_0+\epsilon I_1-\mu I_0-cI_0-\alpha I_0\\ \dfrac{dE_1}{dt}\leq\beta S_1^0I_0+\beta_1S_1^0I_1-dE_1-vE_1-\sigma_1E_1-lE_1-p_1E_1\\ \dfrac{dI_1}{dt}=\sigma_1E_1-dI_1-\epsilon I_1-kI_1\end{cases}$$

for $t\geq0$. Consider the following auxiliary system:

$$\begin{cases}\dfrac{d\tilde{E_0}}{dt}=l\tilde{E_1}+\beta_0S_0^0\tilde{I_0}-(\mu+c+\sigma_0+p_0)\tilde{E_0}\\ \dfrac{d\tilde{I_0}}{dt}=\sigma_0\tilde{E_0}+\epsilon\tilde{I_1}-(\mu+c+\alpha)\tilde{I_0}\\ \dfrac{d\tilde{E_1}}{dt}=\beta S_1^0\tilde{I_0}+\beta_1S_1^0\tilde{I_1}-(d+v+l+\sigma_1+p_1)\tilde{E_1}\\ \dfrac{d\tilde{I_1}}{dt}=\sigma_1\tilde{E_1}-d\tilde{I_1}-\epsilon\tilde{I_1}-k\tilde{I_1}\end{cases}\tag{4}$$

Since $R_0<1$, (0, 0, 0, 0) of system (4) is a global attractor. By the comparison principle, we can conclude that $\lim_{t\to+\infty}E_i(t)=0$ and $\lim_{t\to+\infty}I_i(t)=0$, it follows that $\lim_{t\to+\infty}S_i(t)=S_i^0$ and $\lim_{t\to+\infty}V_i(t)=V_i^0$, $i=0,1$. Therefore, model (1) is an asymptotically autonomous system with limit affine system

$$\begin{cases}\dfrac{dS_0}{dt}=lS_1-(\mu+c)S_0+\delta_1V_0\\ \dfrac{dI_0}{dt}=lV_1-(\mu+c+\delta_1)V_0\\ \dfrac{dE_1}{dt}=A-(d+v+l)S_1+\delta_2V_1\\ \dfrac{dI_1}{dt}=vS_1-(d+l+\delta_2)V_1\end{cases}\tag{5}$$

It is known that the positive equilibrium $(S_0^0,V_0^0,S_1^0,V_1^0)$ of (5) is globally asymptotically stable. This completes the proof. □

Next, let $\Phi_t(x)=\Phi(t,x(t))$ be the continuous flow on X generated by the solution $x(t)$ of model (1) with initial condition $x(0)=(S_0(0),E_0(0),I_0(0),V_0(0),S_1(0),E_1(0),I_1(0),V_1(0))\in X$. $\omega(y)=\bigcap_{t\geq0}\overline{\Phi([t,\infty)\times\{y\})}$, ∂X is the boundary of X, and Ω is the maximal invariant set of $\Phi_t(x)$ on ∂X. We have the following result.

Theorem 2. *If $R_0>1$, then the flow $\Phi_t(x)$ on X is uniformly persistent for any solution $x(t)$ with $S_i(0),V_i(0)>0, i=0,1$, and $E_0(0),I_0(0)>0$ or $E_1(0),I_1(0)>0$.*

Proof. Let

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

$$Y=\{x=(S_0,E_0,I_0,V_0,S_1,E_1,I_1,V_1)\in\partial X;\ \Phi_t(x)\in\partial X,\forall t>0\}$$

By analyzing model (1), we know that Ω consists of a unique equilibrium P_0 on the boundary of X. Thus, $\{P_0\}$ represents an acyclic covering for Ω.

We analyze the behavior of any solution $x(t)$ of model (1) close to P_0. We divide the initial conditions into two cases.

(i) If $I_i(0)=E_i(0)=0, i=0,1$, then $E_i(t)=I_i(t)\equiv 0, i=0,1$. Model (1) implies that $(S_i(t),V_i(t)), i=0,1$, goes away from P_0 as $t\to-\infty$.

(ii) If $E_0(0),I_0(0)>0$ or $E_1(0),I_1(0)>0$, then $E_0(t),I_0(t)\geq 0$ or $E_1(t),I_1(t)\geq 0$ for all $t>0$. When $x(t)$ stays close to P_0, by model (1) there exists some ρ such that

$$\begin{cases} \dfrac{dE_0}{dt}>\tilde{a}_{11}E_0+\tilde{a}_{12}E_1+\tilde{a}_{13}I_0+0 \\ \dfrac{dE_1}{dt}>0+\tilde{a}_{22}E_1+\tilde{a}_{23}I_0+\tilde{a}_{24}I_1 \\ \dfrac{dI_0}{dt}>\tilde{a}_{31}E_0+0+\tilde{a}_{33}I_0+\tilde{a}_{34}I_1 \\ \dfrac{dI_1}{dt}>0+\tilde{a}_{42}E_1+0+\tilde{a}_{44}I_1 \end{cases} \tag{6}$$

where $\tilde{a}_{11}=-M_1-\rho, \tilde{a}_{12}=l-\rho, a_{13}=\beta_0S_0^0-\rho, \tilde{a}_{22}=-M_5-\rho$, $\tilde{a}_{23}=\beta S_1^0-\rho$, $\tilde{a}_{24}=\beta_1S_1^0-\rho$, $\tilde{a}_{31}=\sigma_0-\rho, \tilde{a}_{33}=-M_2-\rho, \tilde{a}_{34}=\epsilon-\rho, \tilde{a}_{42}=\sigma_1-\rho, \tilde{a}_{44}=-M_6-\rho$, and the largest eigenvalue of the matrix $\tilde{A}(\tilde{a}_{ij})$ in (6) is positive, since $R_0>1$ (Diekmann et al., 1990). Hence, the solutions of the linear quasi-monotonic system

$$\begin{cases} \dfrac{dx_0}{dt}=\tilde{a}_{11}x_0+\tilde{a}_{12}x_1+\tilde{a}_{13}y_0 \\ \dfrac{dx_1}{dt}=\tilde{a}_{22}x_1+\tilde{a}_{23}y_0+\tilde{a}_{24}y_1 \\ \dfrac{dy_0}{dt}=\tilde{a}_{31}x_0+\tilde{a}_{33}y_0+\tilde{a}_{34}y_1 \\ \dfrac{dy_1}{dt}=\tilde{a}_{42}x_1+\tilde{a}_{44}y_1 \end{cases}$$

with $x_i,y_i>0, i=0,1$ are exponentially increasing as $t\to\infty$. By the comparison principle, (E_0,E_1,I_0,I_1) goes away from (0, 0, 0, 0). Therefore, $\{P_0\}$ is an isolated invariant set of the flow $\Phi_t(x)$. Using Theorem 4.3 in Freedman et al. (1994), model (1) is uniformly persistent. This completes the proof. ☐

Remark 3. The semiflow $\Phi_t(x)$ we defined above is point dissipative, all the solutions of the system are ultimately bounded in X, and disease is uniformly persistent if $R_0>1$ from Theorem 2. Thus, by a well known result in persistence theory (see Hutson and Schmitt, 1992; Zhao, 2003) we know that the system has at least one positive equilibrium $P^*=(S_0^*,E_0^*,I_0^*,V_0^*,S_1^*,E_1^*, I_1^*,V_1^*,S_h^*,E_h^*, I_h^*,V_h^*)$. However, since there are 12 equations in the model, we are unable to express P^* explicitly and determine its stability.

4. Data simulations and sensitivity analysis

In this section, we simulate the reported human rabies data from Guangdong Province, China, and carry out some sensitivity analysis on some parameters.

From the Department of Health of Guangdong Province, we can obtain the data on human rabies cases. However, the data involving dogs cannot be acquired easily since there are very few published studies on the population dynamics of dogs. Thus, we rely on reality to make some rational assumptions or data fitting. The values of parameters are listed in Table 2. In Guangdong Province, there are two million dogs on rabies exposure every year (He et al., 2009), the vaccination rate is only 32.8% or less, hence we estimate that the number of vaccinated dogs is 0.6 million, so $V_h(0)=6\times10^5$. $I_h(0)=3.87\times10^2$, we make the data fitting to obtain that $E_h(0)=7.13\times10^2$, then $S_h(0)=7.988\times10^7$ (GSY, 2010b); there are about three million dogs and four hundred thousand rabies vaccines every year (Si et al., 2007), thus, we estimate $V_1(0)=6\times10^5, S_1(0)=2.4\times10^6$ and assume $S_0(0)=4\times10^4, E_0(0)=4\times10^2$, $I_0(0)=2.04\times10^3, V_0(0)=0$, and data fitting gives $E_1(0)=2.9\times10^4, I_1(0)=2\times10^4$.

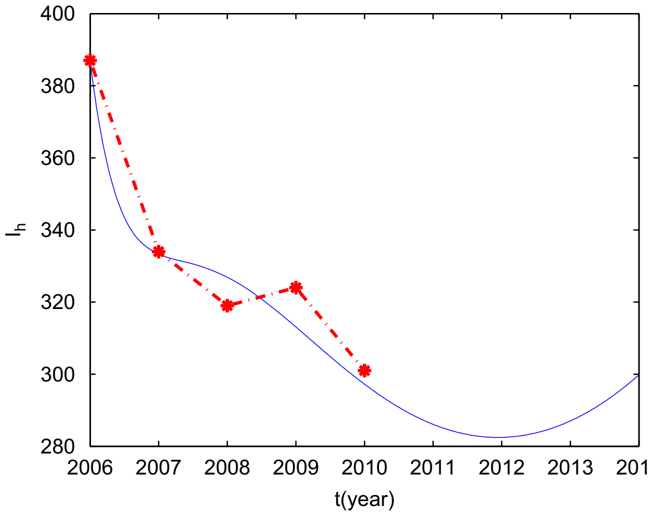

Fig. 2. Simulation of human rabies infection cases over time for Guangdong Province of China. The smooth curve represents the solution I_h of models (1) and (2) and the stars are the reported data on human cases.

Using models (1) and (2), we simulate the data from 2006 to 2010 and predict the trend of human rabies infection in Guangdong Province. Fig. 2 shows that the simulation of our model with reasonable parameter values provides a good match to the data on infected human rabies cases in Guangdong Province from 2006 to 2010. With the current control measures, our model predicts that the human rabies infection cases would continue decreasing in the next a couple of years and then may increase slightly afterward. With the simulated parameter values, we estimate that $R_0=1.65$. Thus, human rabies will persist in Guangdong Province under the current control and prevention measures.

If we fix all parameters except l (the rate at which domestic dogs are abandoned) and ϵ (the rate rabid domestic dogs become stray dogs), the basic reproduction number R_0 increases as l and ϵ increase. Fig. 3 represents the relationship between R_0 and the quantity of stray dogs. We can see that the influence of parameter ϵ on the basic reproduction number R_0 is greater than that of parameter l, thus, culling domestic infected dogs at the right time can effectively decrease R_0. From Fig. 4, we can also see that culling stray dog population (increasing c) can reduce R_0. Moreover, in order to control rabies, the larger ϵ is, the more important it is to target culling stray dogs.

Though both vaccinating susceptible dogs and culling stray dogs are effective control measures, comparing Fig. 5(a) and (b), we find that R_0 can become less than one if the vaccination rate v is greater than 50% but cannot become less than one even though the culling rate is 100%. Thus, culling stray dogs alone is not a good control measure while vaccination is a more effective one.

Fig. 6 depicts the plots of R_0 in terms of (v,c) and (v,ϵ), respectively. We can see that increasing the vaccination rate and the culling rate of rabid domestic dogs is more effective than increasing the vaccination rate and the culling rate of stray dogs. Therefore, culling of infected dogs and vaccination are most important and effective means to control rabies infection.

5. Discussion

As a zoonotic and incurable disease, rabies has always been given due respect both in human and veterinary medicine. Most rabies cases in China are still diagnosed in dogs which confirms

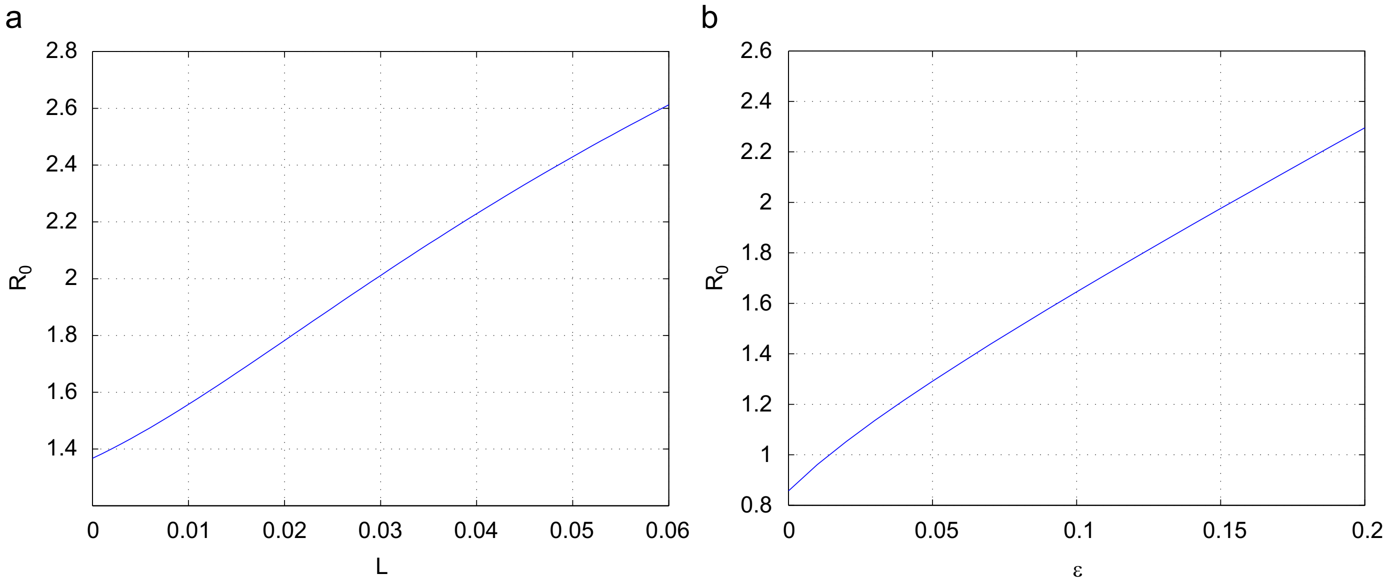

Fig. 3. R_0 in terms of l and ϵ.

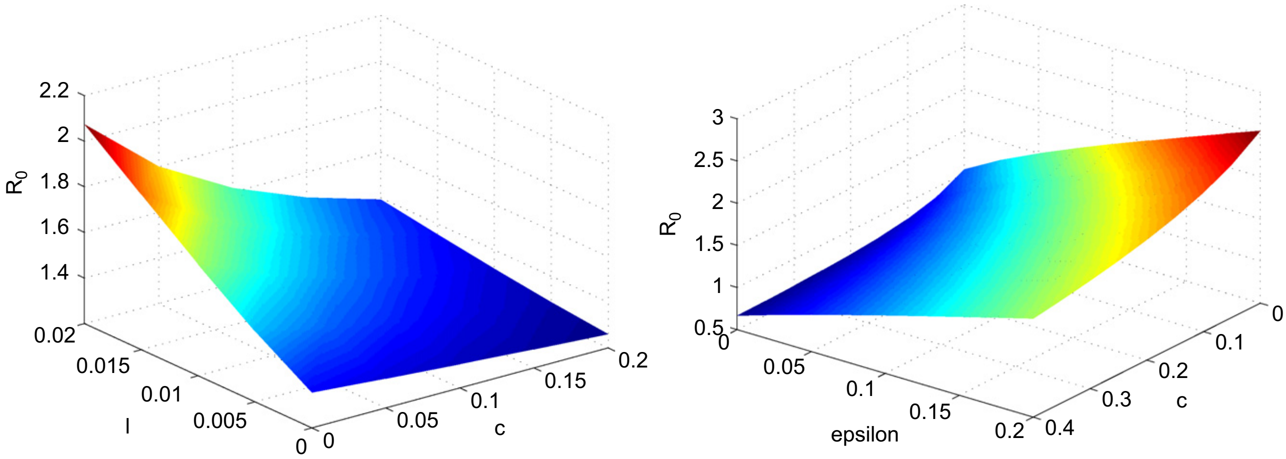

Fig. 4. R_0 in terms of (l,c) and (ϵ,c).

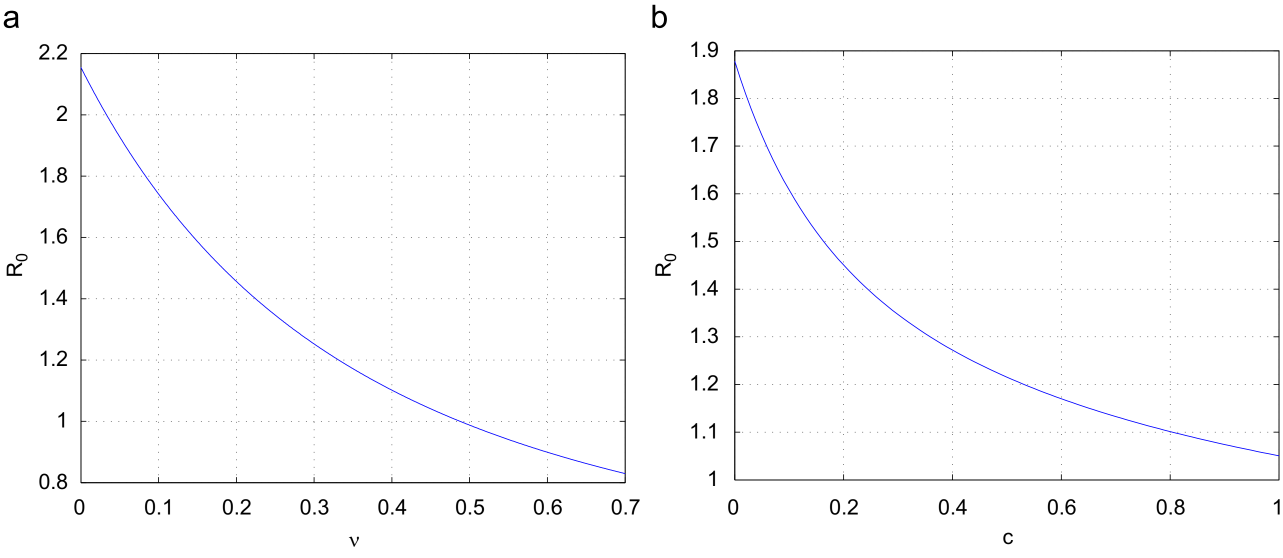

Fig. 5. R_0 in terms of v and c.

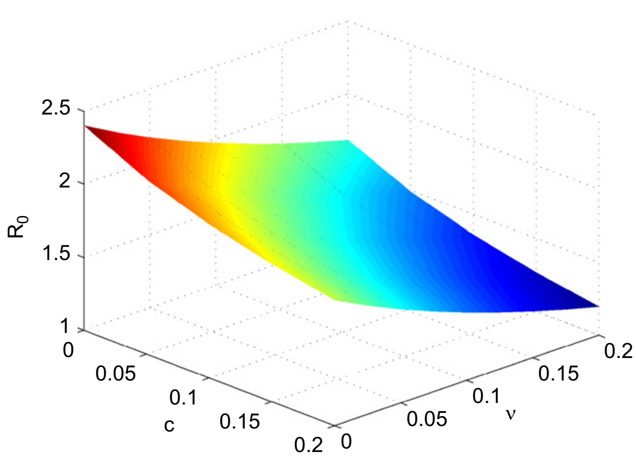

Fig. 6. R_0 in terms of (ν,c) and (ν,ϵ).

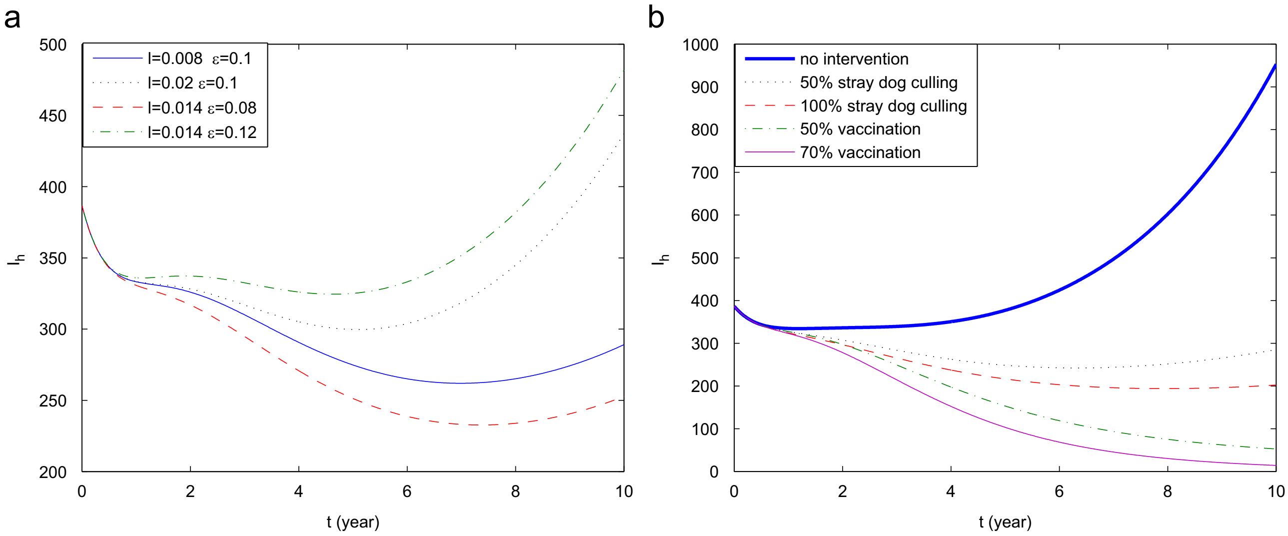

Fig. 7. Simulations of infected human rabies cases I_h on parameters l, ϵ, c and ν in Guangdong Province of China.

the role of the dog as the reservoir and primary perpetrator of the disease. In a recent paper (Zhang et al., 2011), a deterministic model was proposed to study the transmission dynamics of rabies in China. The model consists of susceptible, exposed, infectious, and recovered subpopulations of both dogs and humans and was described by eight ordinary differential equations. The model 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 the immunization of them.

A very important fact that was not considered in Zhang et al. (2011) is that there is a very large number of stray dogs in China. It was reported that at least 18.2% of the human rabies cases in Guangdong Province are caused by stray dogs (Si et al., 2008). In this paper, taking this fact into consideration and using rabies data from Guangdong Province, we proposed an SEIVS model for the dog–human transmission of rabies in which both domestic and stray dogs are considered. The model consists of 12 ordinary differential equations and counts for susceptible, exposed, infectious and recovered domestic dog, stay dog, and human. By the analysis of the model, we concluded that the cases of rabies in Guangdong would decrease gradually in the next a few year and increase slightly afterward, which indicates that rabies cannot be controlled or eradicated under the current strategies. By carrying out some sensitivity analysis of the basic reproduction number in terms of various parameters, we found that the vaccination rate of domestic dogs, the recruitment rate of domestic dogs, the number of stray dogs and the valid time of the immunity play very important roles for the transmission of rabies. From Fig. 7(a), we can see that the acute infection in humans in Guangdong Province would be reduced evidently through the decrease of the stray dog population. Moreover, reducing the transfer from infected domestic dogs to stray dogs is more effective than decreasing domestic dogs that are abandoned. As shown in Figs. 5(a) and 7(b), rabies can be controlled with the vaccination coverage rate over 75% which is a little bit higher than the recommended vaccination rate by WHO, the main reason is that a large number of stray dogs exists in most areas of Guangdong Province. However, from Fig. 7(b), although acute infection cases can be reduced by culling stray dogs, rabies cannot be eventually eradicated by this measure alone. Therefore, culling stray dogs is not a good strategy in controlling rabies. To prevent and control rabies in stray dogs, as suggested in Zhang et al. (2011), fostering of stray dogs could be introduced and encouraged, food baits containing abortifacient oral vaccine in capsules could be distributed in order to reduce the stray dog population and vaccinate stray dogs.

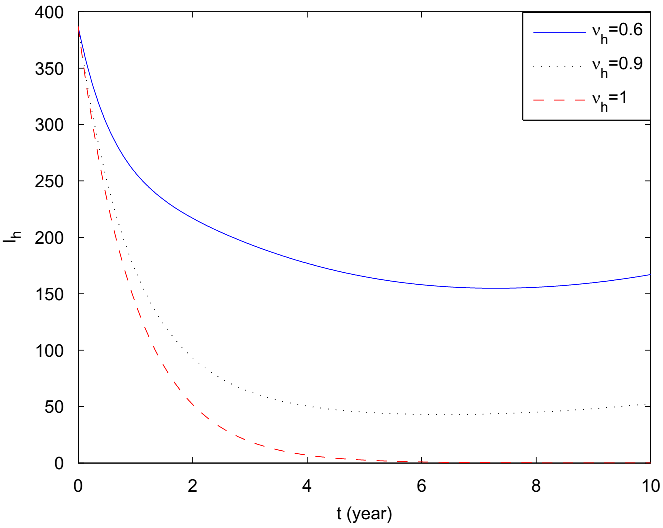

Fig. 8. Simulation of infected human rabies cases I_h on the parameter ν_h in Guangdong Province, China.

The differences between the studies in Zhang et al. (2011) and that in this paper are that only domestic dogs were considered in Zhang et al. (2011) while both domestic and stray dogs are included in model (1) of this paper; Zhang et al. (2011) used the model to simulate the human rabies data from the whole country from 1996 to 2010 while we employ model (1) to simulate the human rabies data from Guangdong Province from 2006 to 2010. We should point out that the latter is the reason that the basic reproduction number for rabies in China was estimated to be $R_0 = 2$ in Zhang et al. (2011) while in this study it is estimated that $R_0 = 1.65$ for Guangdong Province. Indeed, the human rabies cases increased continuously and dramatically in China from 1996 to 2006 and then started to decrease steadily (see Fig. 2 in Zhang et al., 2011). In another study (Zhang et al., submitted for publication) we used the data from 2004 to 2010 for the whole country and it was estimated that the “average” basic reproduction number for China for this time period is $R_1 = 1.25$. These results indicate that human rabies in Guangdong Province is more severe than the average in China.

According to WHO, as long as victims bitten by animals receive proper PEP timely, human rabies can be prevented (Wang, 2002). Fig. 8 indicates that the rabies infection rate can be reduced with the increase of using PEP. Thus, publicity and education on the risk and prevention of rabies is necessary and important to control the epidemic and should be strengthened in endemic areas, especially in rural areas.

In summary, only when both animal rabies surveillance and control and human PEP are emphasized and strengthened at the same time, the serious human rabies epidemic in Guangdong Province of China could be effectively controlled. We also would like to point out that our model may be applied to study the rabies spread in other regions, such as the provinces of Guangxi, Hunan, Guizhou, etc., where rabies is endemic.

There are some limitations in this study. Firstly, the influence of season was not included in the model, while rabies may have different infection rates and different transmission patterns in different seasons (see Zhang et al., submitted for publication). Secondly, dog rabies surveillance often has not been carried out systematically because dog is not an important economic animal in China, the data was limited. Thirdly, dispersal was not taken into account in the model. Future studies should consider seasonality and dispersal in the model. Moreover, more detailed data need to be collected so that the model parameters can be measured or estimated more accurately. We leave these for future consideration.

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References

Allen, L.J.S., Flores, D.A., Ratnayake, R.K., Herbold, J.R., 2002. Discrete-time deterministic and stochastic models for the spread of rabies. Appl. Math. Comput. 132, 271–292.

Artois, M., Langlais, M., Suppo, C., 1997. Simulation of rabies control within an increasing fox population. Ecol. Model. 97, 23–34.

Bohrer, G., Shem-Tov, S., Summer, E., Or, K., Saltz, D., 2002. The effectiveness of various rabies spatial vaccination patterns in a simulated host population with clumped distribution. Ecol. Model. 152, 205–211.

CCDC, 2006. Chinese Center for Disease Control and Prevention, Questions and Answers about Rabies 〈http://www.chinacdc.cn/jkzt/crb/kqb/kqbzstd/200605/t20060522_24185.htm〉.

Clayton, T., Duke-Sylvester, S., Gross, L.J., Lenhartd, S., Real, L.A., 2010. Optimal control of a rabies epidemic model with a birth pulse. J. Biol. Dyn. 4, 43–58.

DOHG, 2010. Department of Health of Guangdong Province, Bulletins 〈http://www.gdwst.gov.cn/a/yiqingxx/〉.

Diekmann, O., Heesterbeek, J.A.P., Metz, J.A.J., 1990. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. J. Math. Biol. 28, 365–382.

Ding, W.-D., Gross, L.J., Langston, K., Lenhart, S., Real, L.A., 2007. Rabies in raccoons: optimal control for a discrete time model on a spatial grid. J. Biol. Dyn. 1, 379–393.

Fooks, A.R., 2005. Rabies in Europe—editorial. Eurosurveillance 10, 1–4.

Freedman, H.I., Ruan, S., Tang, M., 1994. Uniform persistence and flows near a closed positively invariant set. J. Dyn. Differential Equations 6, 583–600.

GSY, 2010a. Guangdong Statistical Yearbook (Main Population Indicators) 〈http://www.gdstats.gov.cn/tjnj/table/4/c4_1.htm〉.

GSY, 2010b. Guangdong Statistical Yearbook (Status of Natural Population Changes) 〈http://www.gdstats.gov.cn/tjnj/table/4/c4_2.htm〉.

Hampson, K., Dushoff, J., Bingham, J., Brückner, G., Ali, Y.H., Dobson, A., 2007. Synchronous cycles of domestic dog rabies in sub-Saharan Africa and the impact of control efforts. Proc. Natl. Acad. Sci. USA 104, 7717–7727.

Harnos, A., Reiczigel, J., Solymosi, N., Vattay, G., 2006. Analysis of the effect of immunization in rabies time series. J. Theor. Biol. 240, 72–77.

He, J.-F., Kang, M., Li, L.-H., Liang, W.-J., 2009. Exposure to human rabies and the related risk factors in Guangdong. Chin. J. Epidemiol. 30, 532–533. (in Chinese).

Hu, R.-L., Fooks, A.R., Zhang, S.-F., Liu, Y., Zhang, F., 2008. Inferior rabies vaccine quality and low immunization coverage in dogs (Canis familiaris) in China. Epidemiol. Infect. 136, 1556–1563.

Hu, R.-L., Tang, Q., Tang, J., Fooks, A.R., 2009. Rabies in China: an update. Vector Borne Zoonotic Dis. 9, 1–12.

Hutson, V., Schmitt, K., 1992. Permanence and the dynamics of biological systems. Math. Biosci. 111 (1992), 1–71.

Knobel, D.L., Cleaveland, S., Coleman, P.G., Fevre, E.M., Meltzer, M.I., Miranda, M.E.G., Shaw, A., Zinsstag, J., 2005. Re-evaluating the burden of rabies in Africa and Asia. Bull. WHO 83, 360–368.

Langlais, M., Suppo, C., 2000. A remark on a generic SEIRS model and application to cat retroviruses and fox rabies. Math. Comput. Model. 31, 117–124.

MOHC, 2009. Ministry of Health of the People's Republic of China, The Status of Prevention and Control of Rabies in China (Zhongguo Kuangquanbing Fangzhi Xiankuang) 〈http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohbgt/s9513/200909/42937.htm〉.

MOHC, 2010. Ministry of Health of the People's Republic of China, Bulletins 〈http://www.moh.gov.cn/publicfiles/business/htmlfiles/wsb/pyqxx/list.htm〉.

Murray, J.D., Seward, W.L., 1992. On the spatial spread of rabies among foxes with immunity. J. Theor. Biol. 156, 327–348.

Rhodes, C.J., Atkinson, R.P.D., Anderson, R.M., Macdonald, D.W., 1998. Rabies in Zimbabwe: reservoir dogs and the implications for disease control. Philos. Trans. R. Soc. London Ser. B 353, 999–1010.

Shi, X.-R., 2005. Zoonotic disease—rabies. Bull. Biol. Chin. 40 (12), 17–18.

Si, H., Guo, Z.-M., Hao, Y.-T., Liu, Y.-G., Zhang, D.-M., Rao, S.-Q., Lu, J.-H., 2008. Rabies trend in China (1990–2007) and post-exposure prophylaxis in the Guangdong Province. BMC Infect. Dis. 8, 113.

Si, H., Liu, Y.-G., Li, G.-W., Liu, Z.-Y., Lu, J.-H., 2007. Analysis on the characteristic of rabies epidemiology in Guangdong Province from 1990 to 2005. J. Sun Yat Sen Univ. (Med. Sci.) 28, 263–264. (in Chinese).

Smith, G.C., Cheeseman, C.L., 2002. A mathematical model for the control of diseases in wildlife populations: culling, vaccination and fertility control. Ecol. Model. 150, 45–53.

Song, M., Tang, Q., Wang, D.-M., Mo, Z.-J., Guo, S.-H., Li, H., Tao, X.-Y., Rupprecht, C.E., Feng, Z.-J., Liang, G.-D., 2009. Epidemiological investigations of human rabies in China. BMC Infect. Dis. 9, 210.

Tischendorf, L., Thulke, H.-H., Staubach, C., Müller, M.S., Jeltsch, F., Goretzki, J., Selhorst, T., Müller, T., Schlüter, H., Wissel, C., 1998. Chance and risk of controlling rabies in large-scale and long-term immunized fox populations. Proc. R. Soc. London Ser. B 265, 839–846.

van den Driessche, P., Watmough, J., 2002. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Biosci. 180, 29–48.

Wang, Z.-X., 2002. WHO position on rabies vaccine. Int. J. Biol. 25, 245–248.

WHO, 1999. World Survey of Rabies for 1998. Geneva.

WHO, 2005. WHO expert consultation on rabies: first report. WHO Technical Report Series 931, pp. 1–121.

Wu, X., Hu, R., Zhang, Y., Dong, G., Rupprecht, C.E., 2009. Reemerging rabies and lack of systemic surveillance in People's Republic of China. Emerg. Infect. Dis. 15, 1159–1164.

Zhang, J., Jin, Z., Sun, G.-Q., Zhou, T., Ruan, S., 2011. Analysis of rabies in China: transmission dynamics and control. PLoS ONE 6 (7), e20891. doi:10.1371/journal.pone.0020891.

Zhang, J., Jin, Z., Sun, G.-Q., Sun, X.-D., Ruan, S. Modeling seasonal rabies epidemics in China, submitted for publication.

Zhang, Y.-Z., Xiao, D.-L., Sun, Y.-H., Yang, X.-R., Yan, Y.-Z., 2003. The epidemic situation of human rabies from 1984 to 2002 and its preventive measures in China. Chin. J. Epidemiol. 24, 883–886.

Zhao, X., 2003. Dynamical Systems in Population Biology. Springer, New York.

Zinsstag, J., Dürra, S., Penny, M., Mindekem, R., Roth, F., Menendez Gonzalez, S., Naissengar, S., Hattendorf, J., 2009. Transmission dynamics and economics of rabies control in dogs and humans in an African city. Proc. Natl. Acad. Sci. USA 106, 14996–15001.