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Dynamic analysis of rabies transmission and elimination in mainland China

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ABSTRACT

Rabies is an acute zoonotic infectious disease caused by rabies virus. In 2015, the World Health Organization proposed the goal of eliminating dog-induced human rabies by 2030. In response to this goal positively, China has been dedicated to the control and elimination of rabies mainly caused by dogs, for nearly 10 years. By applying infectious disease dynamics, in this paper, we establish a dog-human rabies transmission model to forecast future epidemic trends of rabies, assess whether the goal of eliminating dog-induced human rabies cases in China can be achieved in 2030, and further evaluate and suggest the follow-up sustained preventive measures after the elimination of human rabies. By analyzing and simulating above dynamic model, it is concluded that rabies has been well controlled in China in recent years, but dog-induced human rabies cannot be eliminated by 2030 according to current situation. In addition, we propose to improve rabies control efforts by increasing the immunization coverage rate of rural domestic dogs, controlling the number of stray dogs and preventing the import of rabies virus in wild animals. Immunization coverage rate of rural domestic dogs which is currently less than 10% is far from requirement, and it needs to reach 50%–60% to meet the goal of 2030. Since it is difficult to immunize stray dogs, we suggest to control the number of stray dogs below 15.27 million to achieve the goal. If the goal of eliminating human rabies is reached in 2030, the essential immunization coverage needs to be maintained for 18 years to reduce the number of canine rabies cases to zero. Lastly, to prevent transmission of rabies virus from wild animals to dogs, the thresholds of the number of dogs and the immunization coverage rate of dogs after eliminating canine rabies cases are also discussed.

1. Introduction

Rabies is an acute zoonotic infectious disease caused by rabies virus [1]. The host animals of rabies virus in nature include dogs, cats, and wild animals such as wolves, foxes, jackals, bats, raccoons, skunks, etc. [2]. After human are bitten by a rabid animal, they will show a series of symptoms such as hydrophobia, photophobia and pharyngeal spasm, and the mortality rate is 100% [3]. Rabies has become endemic in more than 150 countries around the world [4], and more than 59,000 people die of rabies every year, of which more than 99% occur in Asia and Africa. In China, more than 95% of human rabies cases are infected through the bite of an infected dogs [5]. Rabies has been classified as a class II infectious disease in the National Stationary Notifiable Communicable Diseases, and the number of deaths caused by the epidemic lists in the forefront of infectious diseases, which has seriously threatened the lives safety of people [6]. As shown in Fig. 1, the last epidemic peak of human rabies was in 2007, with 3300 cases [7]. After that, the number of human cases has dropped every year, and decreased to 202 in 2020 [1].

Although the fatality rate of rabies is extremely high, it is an infectious disease that can be prevented and controlled through scientific and effective measures [8,9]. To eliminate human rabies, the transmission of

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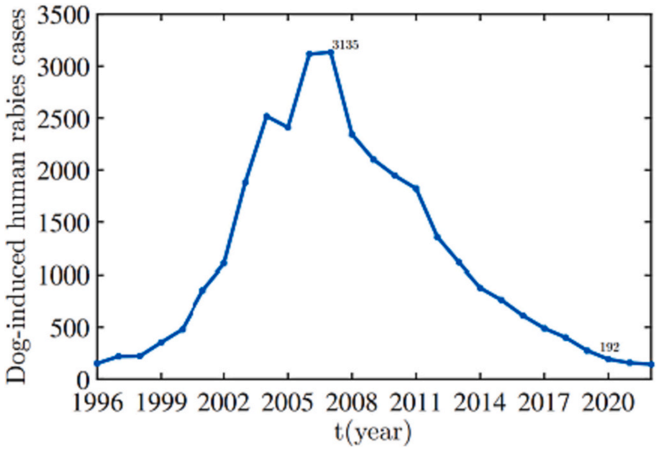

Fig. 1. Dog-induced human rabies cases in China from 1996 to 2022. Dog-induced human rabies cases account for 95% of the total human cases.

rabies virus among animals, mainly dogs, must be contained. Improving the immunization coverage rate of dogs, strengthening the management of dogs and enhancing the awareness of human prevention can prevent the transmission of rabies virus between dogs and dogs to humans, and effectively reduce the incidence of rabies. According to the World Health Organization, the immunization coverage rate of dogs in one area need be above 70%, which can effectively stop the transmission of rabies [10]. Rabies has been completely eliminated in Australia, Singapore and other countries [11,12]. In 2019, Mexico became the first country in the world to be recognized as having eliminated human deaths from dog-induced human rabies by the World Health Organization [13]. Subsequently, dog-induced human rabies is also gradually under control in many countries. Moreover, human rabies cases can be reduced by decreasing the number of stray dogs. In recent years, more and more pet dogs have been abandoned and turned into stray dogs, and the mating of stray dogs is not controlled by human beings, resulting in more and more stray dogs, and stray dogs are difficult to be immunized. Therefore, it is important to strengthen the management of dogs [14]. Based on the monthly data of human rabies cases reported by the Chinese Ministry of Health, the cases in the summer and autumn are significantly higher than in the spring and winter. In summer and autumn, light clothing is less protective against dog bites, especially farmers, who have frequent outdoor activities and have greater contact with dogs. In addition, from July to September schools are closed for summer vacations and children are out of supervision and enjoy tantalizing dogs. Thus, it is essential to enhance people's awareness of prevention [15].

In the past 15 years, China has made remarkable progress in the prevention and control of rabies. The number of deaths related to human rabies has declined significantly, which mainly relied on mass vaccination and the improvement of public awareness of post-exposure prophylaxis [11]. China has underwent a dramatic increase in the number of dogs in recent decades, with a relative decrease in the number of dogs in rural areas and an increase in urban areas. For rural areas, dogs are used to guard the house, but now greatly strengthened anti-theft devices in rural areas and the prevalence of surveillance cameras have reduced the demand for house-watching dogs. In addition, for the better education for children, the convenience of work, the pursuit of living standards and other reasons, many people choose to move to live and work in cities, resulting in a decrease in the number of rural population and rural dogs. For the city, with the development of economy, people begin to seek spiritual sustenance, and dogs are owned as pets and play the role of children's "partner", which makes the number of pet dogs gradually increase. At the same time, with the enhancement of people's awareness of rabies and the management of dogs, especially in urban areas, many dog owners have registered and vaccinated their dogs, which has greatly improved the immunization coverage rate of urban pet dogs. However, rural dog owners are still weak in awareness and unwilling to pay the vaccine cost, so the vaccination rate of rural dogs is still very low [6]. Regarding to stray dogs, the population is growing due to abandonment and uncontrolled mating, but they cannot be vaccinated well. In order to decrease the stray dog population, there were a few times of well-known killing-dogs events. In 2006, more than 50,000 dogs were killed in a country in Yunnan Province after three people died of rabies. In 2009, a large number of stray dogs and domestic dogs were also killed after eight people died of rabies in Hanzhong. With above backgrounds, rabies cases in China have been declining for 15 years.

In 2015, the World Health Organization (WHO), the World Organization for Animal Health (OIE), the Food and Agriculture Organization of the United Nations (FAO) and the Global Alliance for Rabies Control held a meeting on rabies in Geneva and proposed the goal of eliminating dog-induced human rabies by 2030 [16]. China actively responds to the call of the World Health Organization and aims to eliminate dog-induced human rabies by 2030. Therefore, based on the current number of dogs and the development trend of rabies in China, to evaluate whether China can achieve the goal of 2030 and which measures should be taken to achieve this goal are urgent issues. It is also necessary to prevent imported dog cases or wild animals cases after the elimination of rabies, which may cause the re-outbreak of dog rabies. Therefore, after the elimination goal is achieved, it is necessary to assess measures to prevent the recurrence of rabies in China. The prediction and evaluation of all these cannot be carried out by experiments, but can be studied by applying mathematical models.

For the spread of infectious diseases, dynamics is one of the most effective measures to study the effectiveness of control measures and predict the epidemic trend. The earliest history of infectious disease dynamics can be traced back to the smallpox model developed by D. Ernoulli in 1760 [17]. In 1911, Ross developed a malaria-mosquito model to study the prevalence and control of malaria. In 1927, Kermack and Mckendrick constructed the famous SIR compartment model to study the spread of the Black Death. In 1932, they proposed the SIS model and the threshold theory, which lay the a foundation for the dynamics of infectious diseases [1]. Based on classical SIS, SIR and SIRS compartment models, dynamical models have been expanded to study the spread of various infectious diseases by considering age structure, time delay and cross-infection in multiple populations and other factors [18–22].

For the spread of rabies, considering the seasonality, spatial heterogeneity and periodicity of rabies epidemic, Zhang et al. established an SEIR mathematical model to compare the effectiveness of control measures through numerical simulation of model and sensitivity analysis of parameter and to propose that immunization is the key measure to control rabies [1,15,23]. Hou et al. proposed a mathematical model to describe the dog-human transmission of rabies and suggested 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 [14]. Liu et al. proposed a two-patch SEIRS epidemic model to study the impact of travel on the spatial spread of dog rabies between patches with different level of disease prevalence [24]. Chen et al. proposed a multi-patch model to describe the transmission dynamics of rabies between dogs and humans in different provinces [25]. Ruan gave a review of models, results and simulation results of rabies transmission in China [6]. Abdulmajid et al. constructed a dynamical model with time delay to study the effect of control strategies and time delay on rabies prevalence [3]. Kotzé et al. constructed an individual-based random transmission model, created a data set containing a combination of factors that may affect the elimination of rabies and analyzed the influence of these factors on the elimination of rabies [18]. Even in disease-free countries, it is important to prevent the invasion of rabies. Hudson et al. employed rabies models to simulate potential outbreaks and evaluate various disease control strategies to improve control of a potential rabies incursion in Australia [26]. Pantha et al. developed a mathematical model to describe the transmission status of rabies in Nepal, evaluated potential control strategies, and proposed that inter-species transmission from jackals to dogs to humans may lead to ongoing prevalence of rabies in Nepal [27].

By means of dynamical model, in this paper, we firstly calculate the reproduction number of rabies and predict the total number of humans and dogs, the development trend of human rabies and the prevalence of rabies among dogs in China. Secondly, by studying the relationship between dog immunization coverage and human rabies cases by 2030, we provide the minimum immunization coverage required to eliminate human cases by 2030, and analyze the impact of immunization coverage rates of urban pet dogs, rural domestic dogs, and stray dogs on human cases in 2030. Thirdly, we study the relationship between stray dog population and the achievement of the goal. Finally, we explore how much prevention and control effort is needed to maintain the zero state after reaching the goal of eliminating human rabies in China.

2. Methods

2.1. Data

The data adopted in this paper include the number of human rabies cases, human population, the number and immunization coverage of urban pet dogs, rural domestic dogs, and stray dogs. Human rabies cases from 2015 to 2022 are available on the website of the Chinese Center for Disease Control and Prevention, 95% of which are dog-induced human rabies cases [28]. The total human population is obtained from China Statistical Yearbook [29]. The number of pet dogs in urban areas in recent years can be obtained in White Paper on China's Pet Industry. The information on the number of dogs in rural areas can be found in the Survey Report on the Status of Dog Survival and Loss in Rural China issued by the Animals Asia. In addition, taking two villages as representatives, we obtain the total number of households and the number of households with dogs, and then deduce the approximate number of rural domestic dogs in China. Lastly, based on online news and information, the number of stray dogs is roughly estimated to exceed 40 million and is increasing every year in China [30].

2.2. Model

This paper only studies the transmission and control of dog-induced rabies, which is main transmission mode of rabies in China, so two groups are considered in this paper: dogs and human. According to the development process of rabies, dogs and humans are divided into four categories: susceptible, exposed, infectious and vaccinated. For the dog population, the number of susceptible individuals, exposed individuals, infectious individuals and vaccinated individuals at time t are denoted by $S(t), E(t), I(t), V(t)$, respectively. Similarly, for human population, the number of susceptible, exposed, infectious and vaccinated persons at time t are denoted by $S_1(t), E_1(t), I_1(t), V_1(t)$, respectively. Susceptible individuals refer to healthy individuals, but are susceptible to infection after contact with rabid dogs. Exposed individuals are those that have been bitten by infectious dogs but have no clinical symptoms and are not infectious. Infectious individuals are those that are infectious and have clinical symptoms such as headache, fatigue, irritability, fear of wind, light, sound and water. Vaccinated individuals have been vaccinated against rabies. The total number of dogs and humans at time t are denoted by $N(t), N_1(t)$, respectively, where $N(t) = S(t) + E(t) + I(t) + V(t)$, $N_1(t) = S_1(t) + E_1(t) + I_1(t) + V_1(t)$. The rabies virus can be transmitted among dogs or from dogs to humans, but cannot be transmitted from people to dogs, or among people. For the dog population, susceptible dogs can become exposed dogs after being bitten by rabid dog. If exposed dogs are with timely vaccination, they can become vaccinated dogs and cannot show clinical symptoms. If the virus in exposed dogs is cleaned up in time, exposed dogs can become susceptible dogs again. On the contrary, If exposed dogs are not vaccinated and the virus in the wound is not cleaned in time, they will develop clinical rabies and eventually die. In addition, as required by the government, susceptible dogs are vaccinated regularly every year, these susceptible dogs will become vaccinated dogs. The immune protection period for rabies is one year. With the end of the protection period, some of vaccinated dogs become susceptible dogs again. Being similar to dogs, human rabies cases has same transmission process. The only difference is that humans get vaccinated only after being bitten by dogs. So, there will exist a situation that some people bitten by healthy dogs will get vaccinated and become vaccinated people. The protection period of human rabies vaccine is only half a year. Fig. 2 shows the flow chart of rabies transmission between dogs and humans.

A and B are average birth number of dog and human per year, respectively. m, m_1 represent the natural death rate of dogs and humans, respectively. μ, μ_1 represent disease-related death rate of dogs and humans, respectively. βrepresents the coefficient of dog-to-dog transmission rate; βSI represents new infected dog number at time t. k represents the vaccination rate. γ represents clinical outbreak rate of exposed dogs; σ represents the reciprocal of the dog incubation period. λ represents the loss rate of antibody in dogs. $C(N)S_1$ represents the number of people bitten by dogs in a year; $\beta_0 C(N) S_1 \frac{I}{N}$ refers to those who are bitten by infectious dogs and have rabies virus in their wounds. Since the contact number of human with dogs has linear relationship with the number of dogs, $C(N) = CN$. Let $\beta_0 C \triangleq \beta_1$, where β_0 represents the probability of having rabies virus in the wound after being bitten by infectious dog. So, $\beta_0 C(N) S_1 \frac{I}{N} = \beta_1 S_1 I$ and it represents new infected human number, and β_1 represents the coefficient of dog-to-human transmission rate. We assume that infectious dogs will certainly deposit rabies virus in the wound after biting, that is, $\beta_0 = 1$. The population who are bitten by healthy dogs can be expressed as $\beta_1 S_1 N - \beta_1 S_1 I$, where p represents the probability to get vaccinated after being bitten by dogs. So $(\beta_1 S_1 N - \beta_1 S_1 I)p$ refers to those who are bitten by healthy dogs and get vaccinated. k_1 represents the reciprocal of the time to complete the immunization program, that is, human vaccination rate; γ_1 represents clinical outbreak rate of exposed people; σ_1 represents the reciprocal of the human incubation period; λ_1 represents loss rate of antibody in human.

Based on above assumption, the established model in the paper is given as follows. The model in this paper is similar to Zhang's paper [1], but it considers the case that rabies vaccines can be used by some susceptible people, which is more reasonable.

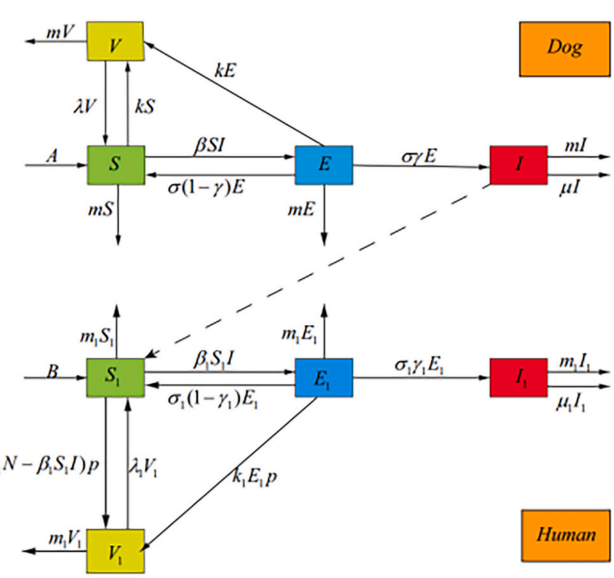

Fig. 2. The flow chart of rabies transmission between dogs and humans.

$$\begin{cases} \frac{dS}{dt} = A + \lambda V + \sigma(1-\gamma)E - \beta SI - (m+k)S, \\ \frac{dE}{dt} = \beta SI - (m+\sigma+k)E, \\ \frac{dI}{dt} = \sigma\gamma E - (m+\mu)I, \\ \frac{dV}{dt} = k(S+E) - (m+\lambda)V, \\ \frac{dS_1}{dt} = B + \lambda_1 V_1 + \sigma_1(1-\gamma_1)E_1 - m_1 S_1 - \beta_1 S_1 I - (\beta_1 S_1 N - \beta_1 S_1 I)p, \\ \frac{dE_1}{dt} = \beta_1 S_1 I - (m_1 + \sigma_1 + k_1 p)E_1, \\ \frac{dI_1}{dt} = \sigma_1\gamma_1 E_1 - (m_1+\mu_1)I_1, \\ \frac{dV_1}{dt} = k_1 E_1 - (m_1+\lambda_1)V_1 + (\beta_1 S_1 N - \beta_1 S_1 I)p. \end{cases} \quad (1)$$

2.3. Model parameters

Most parameter values in model (1) can be taken from literatures, estimated by basing on the actual investigation and communication with professionals. Some parameter values such as A, m_1, β, β_1 that are still unavailable directly, can be estimated by fitting model with actual case data. In this paper, we adopt rabies cases from 2015 to 2022 which can be obtained in Appendix. The definition and values of parameters are shown in Table 1.

Applying the least squares estimation method, we use the total number of dogs to estimate A, use the human population to estimate m_1, and use the human rabies cases to estimate β and β_1. We define $\widetilde{y}(t)$ as the actual number of dogs and $y(t)$ as the theoretical value of the number of dogs in model, which satisfies $\frac{dy(t)}{dt} = A - my(t)$. By constructing the function $f(A) = \sum_{t=2015}^{t=2020}[\widetilde{y}(t) - y(t)]^2$, we apply the *fminsearch* function in MATLAB to get the value of A. In addition, considering that there exists the error for the actual number of dogs with different sources, it is assumed that the number of dogs at time t obeys Poisson distribution, from which 1000 samples are randomly selected to obtain 1000 sets of sample data, where $t = 2015, 2016, \ldots, 2020$. Then, 1000 groups of sample data are respectively fitted to obtain 1000 groups of values of A. Assuming that A follows a normal distribution, its mean and variance can be obtained. According to the data of the National Bureau of Statistics, the average number of annual human birth in China is 14.39 million in recent years, and the actual population data can be obtained from the China Statistical Yearbook [30]. We define $\widetilde{x}(t)$ as the actual number of people and $x(t)$ as the theoretical number of people, which satisfies $\frac{dx(t)}{dt} = B - m_1 x(t)$. Similarly, the natural death rate m_1 can be obtained by the least square estimation. The coefficient of dog-to-dog transmission rate β and dog-to-human transmission rate β_1, also need to be estimated by fitting model with the human rabies cases. Let $y_1(t)$ be the actual reported number of human rabies cases at time t and $y_2(t)$ be the theoretical value of the number of human rabies cases at time t, we randomly take 1000 sets of sample data and construct the objective function $min\sum_{t=2015}^{t=2022}[y_1(t) - y_2(t)]^2$to get the mean and variance of parameter values β and β_1.

From White Paper on China's Pet Industry, we obtain the immunization coverage rate of pet dogs in urban areas to be about 63% in recent years. Immunization coverage rate of rural domestic dogs is low, and it is assumed to be 10%, while stray dogs are hardly vaccinated. Let $k = \varepsilon_a k_a + \varepsilon_b k_b + \varepsilon_c k_c$, where k_a, k_b and $k_c$are the vaccination rate of urban pet dogs, rural domestic dogs and stray dogs respectively, and $k_a = 0.63$, $k_b = 0.1, k_c = 0$; $\varepsilon_a, \varepsilon_b$and ε_c are the proportion of pet dogs, rural domestic dogs and stray dogs, respectively, and $\varepsilon_a = 0.25, \varepsilon_b = 0.5, \varepsilon_c = 0.25$. So, in this paper, we assume that the range of vaccination rate $k$is [0.2, 0.3] [31].

Domestic dogs and stray dogs have different life span. Generally, the life span of domestic dogs is 10–15 years, while the average life span of stray dogs generally does not exceed 3 years. This is because stray dogs are more likely to have accidents and encounter food shortages, diseases, etc. In this paper, the life span of domestic dogs is assumed to be 12 years, and that of stray dogs is 3 years [32]. Combined with the number of domestic dogs and stray dogs, the expected life span of dogs is 9.9 years. Then natural death rate of dogs is $\frac{1}{9.9}$, that is $m = 0.1010$. We assume that the dog loss rate of antibody is 50% [14]. Since clinical outbreak rate of human being bitten by rabid dog is related to the site of the bite, we assume that $\gamma = 0.19$ [33]. After being bitten by rabid dog, five doses of rabies vaccine should be given for human within a month, so the vaccination rate of human is 12, that is, $k = 12$ [34]. In 2020, people's awareness of self-protection has been increasing and the ratio of completing whole-process vaccination after exposure has reached 85%. We assume that the probability of people to be vaccinated after being bitten by a dog is 85%–95%, so$p$is [0.85,0.95]. Generally,

Table 1
Definition and values of parameters in model (1).

Parameters	Values	Definition	Source
A	$N\left(2.5284\times10^7, (7.7205\times10^4)^2\right)$	Annual dog newborn puppies	Fitting
λ	0.5	Dog loss rate of antibody	[29]
γ	0.19	Clinical outbreak rate of dogs	[33]
σ	6	Reciprocal of dog incubation period	[1]
$\frac{1}{\sigma}$	$\frac{1}{6}$	Dog incubation period	[1]
m	0.1010	Natural death rate of dogs	[32]
β	$N\left(9.3238\times10^{-7}, (3.6629\times10^{-8})^2\right)$	Dog-to-dog transmission rate coefficient	Fitting
k	[0.2,0.3]	Dog vaccination rate	[31]
μ	24	Dog disease-related death rate	[35]
B	1.439×10^7	Annual human birth population	[29]
λ_1	1	Human loss rate of antibody	[1]
γ_1	0.19	Clinical outbreak rate of human	[33]
σ_1	6	Reciprocal of human incubation period	[1]
$\frac{1}{\sigma}$	$\frac{1}{6}$	Human incubation period	[1]
m_1	0.0065	Natural death rate of humans	Fitting
β_1	$N\left(3.3749\times10^{-11}, (2.8600\times10^{-12})^2\right)$	Dog-to-human transmission rate coefficient	Fitting
p	[0.85,0.95]	Probability of human vaccination	Assumption
k_1	12	Human vaccination rate	[34]
μ_1	1	Human disease-related death rate	[1]

infectious dogs will die within half a month, so we assume that dog disease-related death rate is 24, that is $\mu = 24$ [35].

By applying model (1), we simulate human rabies cases from 2015 to 2022 in China. Fig. 3 shows that the simulation result of model with reasonable parameters values provides a good match to the data on human rabies cases in China from 2015 to 2022, which verifies the rationality of the model in this paper.

3. Results

3.1. Reproduction number

The basic reproduction number R_0, is a key quantity to assess transmissibility of infectious diseases. We can take it to measure the average number of secondary infections caused by a single infectious individual during the mean infectious period in an entirely susceptible population [36]. As a threshold, it determines whether the disease will become endemic or disappear with time. If $R_0 < 1$, the epidemic will disappear with time; If $R_0 > 1$, an epidemic will spread and become endemic in population. One of the best known practical application of R_0 is to determine the critical values of parameters required to eradicate a disease in a randomly mixing population. R_0 is suitable for infectivity assessment of the initial stage of the epidemic. Moreover, it is of practical importance to evaluate time-dependent transmission potential of rabies virus, which can be assessed by the effective reproduction number $R(t)$, defined as the average number of secondary cases caused by primary case at time t during the mean infection period. $R(t)$ can show the variation of transmissibility with time due to the implementation of control measures. If $R(t) < 1$, it suggests that the epidemic is in decline. If $R(t) > 1$, it suggests that the disease will continue to spread [37].

3.1.1. Basic reproduction number

By observing model (1), we can see that the first four equations are independent of the last four equations, so only the first four equations need to be considered to discuss the dynamical behavior of model, which are the same as the first four equations in Zhang's paper [1]. In Zhang's paper, the expression of basic reproduction number has been calculated as.

$$R_0 = \frac{\beta S^0 \sigma \gamma}{(m+\mu)(m+k+\sigma)}, \text{Where } S^0 = \frac{A(m+\lambda)}{m(m+k+\lambda)}.$$

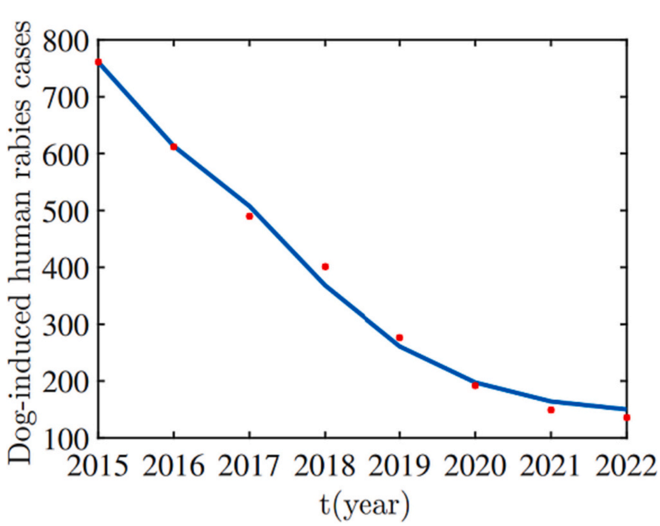

Fig. 3. The fitting chart of dog-induced human rabies cases from 2015 to 2022. The red dots represent the data reported by the Chinese Center for Disease Control and Prevention while the solid curve represents the fitting result of model. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The mean and range of R_0 can be obtained with parameter values in Table 1. The basic reproduction number of rabies is about 1.2278, with the range of [1.2224,1.2332], which reveals that the rabies among dogs cannot be controlled yet. The continuous decline of human cases from 2015 to 2022 is due to the fact that the amount of usage of human rabies vaccine has increased significantly.

3.1.2. Effective reproduction number

With the development of the disease, susceptible population will change with implementation of control measures, which will lead to change of reproduction number with time. The effective reproduction number is introduced and defined as

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

According to parameter values in Table 1, we present the change of effective reproduction number over time in Fig. 4. From 2022 to 2033,$R(t) > 1$ indicates that the epidemic will have a growth tendency over the next few years. From 2033 to 2042, $R(t) < 1$ indicates that the transmissibility of rabies will decrease over time, and finally $R(t)$ tends to 1.

3.2. Number forecasting

Human rabies cases are closely related to the number of people and dogs. To predict the number of rabies cases, we first need to predict the number of people and dogs in the next years. As shown in Fig. 5(a) and Fig. 5(b), the numbers of people size and dogs are both increasing in recent years. But, the ratio of people to dogs is getting smaller, that is, about 7.7 people possess one dog averagely in 2015 and 6.4 people possess one dog in 2025, as shown in Fig. 5(c), which illustrates that the chance of contact between people and dogs is greater with time.

Applying the dynamical model, we predict the number of dog-induced human rabies cases and the prevalence rate of rabies among dogs. As shown in Fig. 6(a), we can see that the number of human rabies cases has been decreasing in recent years. But, after it decreases to a certain extent, it will rise again and finally become stable. As can be seen from Fig. 6(b), at present, the theoretical value of positive rate of canine rabies is 0.54%. Then, it will rise to a small peak value, and finally tends to a steady state about 1.8%. So, we must take more effective prevention and control measures to promote the elimination of rabies.

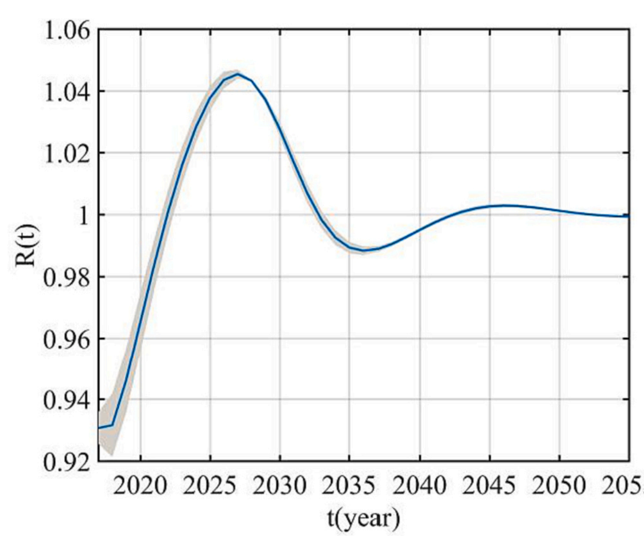

Fig. 4. The change of effective reproduction number with time. The blue line is the mean value, and the gray area is the 95% confidence interval for 100 random simulations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

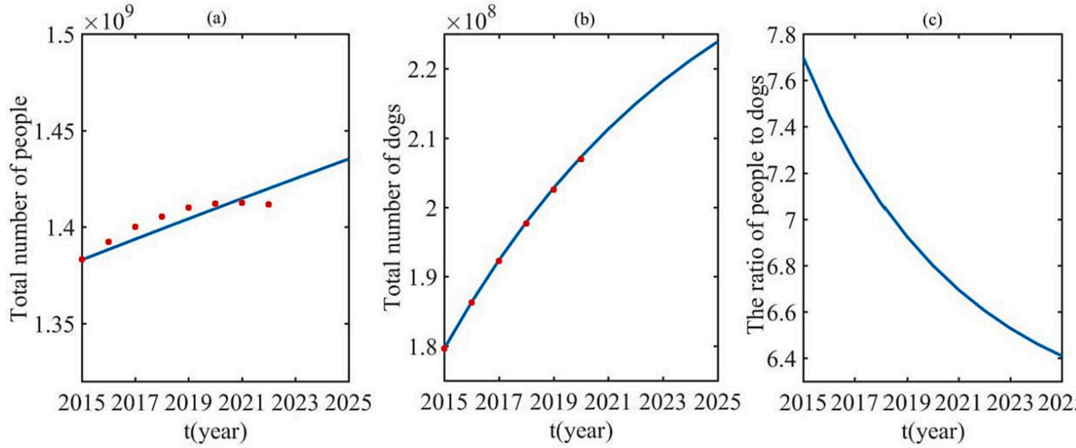

Fig. 5. (a) Prediction of the total number of people in China. (b) Prediction of the number of dogs in China. (c) The ratio of people to dogs.

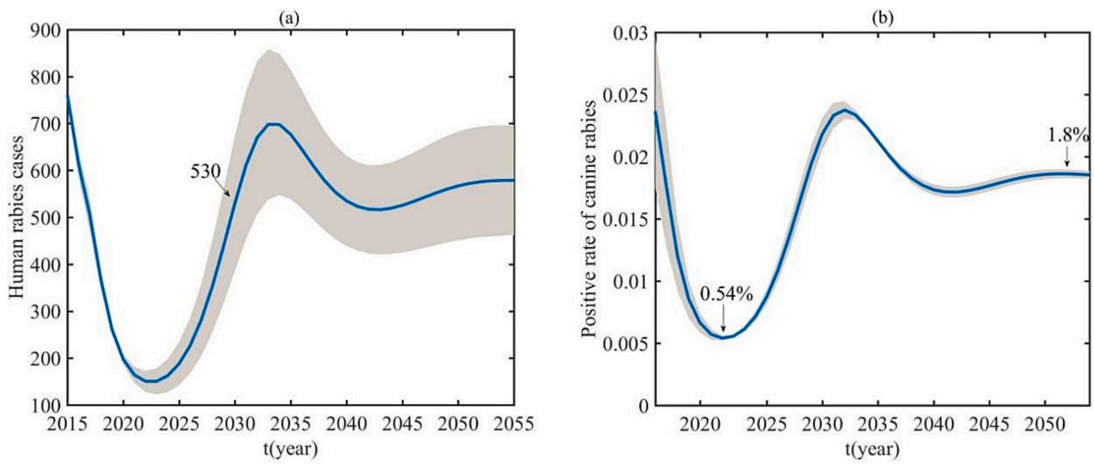

Fig. 6. The prevalence of rabies. (a) The number of human rabies cases. (b)The positive rate of canine rabies.

3.3. Evaluation of elimination goals

From the prediction of rabies in Fig. 6(a), we can observe that it is still difficult to eliminate dog-induced human rabies by 2030 according to the current transmission rate and control efforts.

of rabies in China, and the number of human rabies cases will be about 530 by 2030. Therefore,

more powerful control measures are needed to carry out.

The main measures to eliminate rabies are to increase the immunization coverage rate of dogs, which is currently only 20%–30%, and to

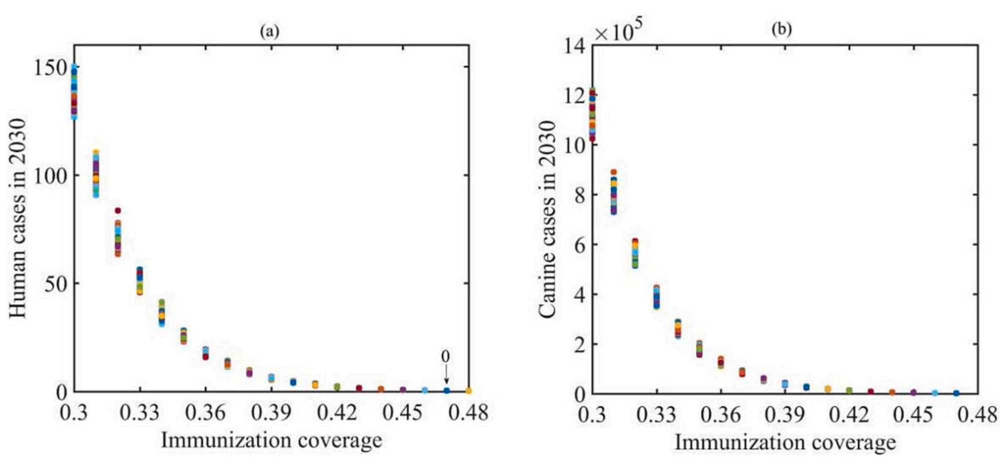

Fig. 7. (a) The relationship between immunization coverage rate of dogs and theoretical human cases number of model in 2030. Dots represent 100 times of predicted number of human rabies cases in 2030 with different immunization coverage rate. (b) The relationship between immunization coverage rate and canine cases in 2030. When immunization coverage rate is 47%, the theoretical number of canine cases in 2030 is in [1886, 2228].

strengthen the management of dogs, especially stray dogs [14,38,39]. As shown in Fig. 7(a), we give the relationship between the immunization coverage rate of dogs and the theoretical number of human cases in 2030. The higher the immunization coverage rate of dogs, the fewer human rabies cases in 2030. It is found that if immunization coverage is increased to 47% from now on, the number of human cases will be almost zero in 2030, indicating that China can achieve the goal of eliminating dog-induced human rabies with 47% immunization coverage from now on.

There are a large number of stray dogs in China, and most of them have not been vaccinated against rabies. It is necessary to strengthen the supervision of stray dogs and curb the occurrence and prevalence of rabies from the source. The proportion of stray dogs can be reduced through the management of stray dogs. As shown in Fig. 8, the smaller the proportion of stray dogs, the smaller the human cases in 2030. When the number of stray dogs is 0, the number of human cases will drop to about 14 in 2030. Therefore, reducing the number of stray dogs is an important measure to control rabies, but it should be combined with the improvement of immunization coverage rate to achieve the goal.

Fig. 9 shows a positive linear relationship between the number of stray dogs and R_0. The transmissibility of rabies decreases with the decrease of the number of stray dogs. When the number of stray dogs is controlled below 15.27 million, $R_0 < 1$, which means that rabies will eventually disappear with time.

3.4. Maintenance and prevention after realizing the goal

For Mexico, there was a serious epidemic in the 1980s. The government conducted a series of mass immunizations that essentially eliminated human rabies in 15 years and brought canine cases to zero in another 11 years. According to this experience, we cannot relax after the elimination of human rabies, since it is just the achievement of initial goals. In order to prevent rebound of human rabies, we need continue to carry out canine immunization after achieving the goal in 2030, which can be called as maintenance stage. The final goal is to reduce the number of canine rabies cases to be zero.

In the previous section, we conclude that increasing the immunization coverage to at least 47% will reduce the number of human rabies cases to zero in 2030. However, at that time, there are still a certain number of dog cases, about 2057, as shown in Fig. 7(b), which may cause human rabies cases to appear again. As can be seen from Fig. 10, if 47% immunization coverage rate is continually maintained, canine cases will drop to zero in 18 years. Then, the canine cases will be eliminated by 2048.

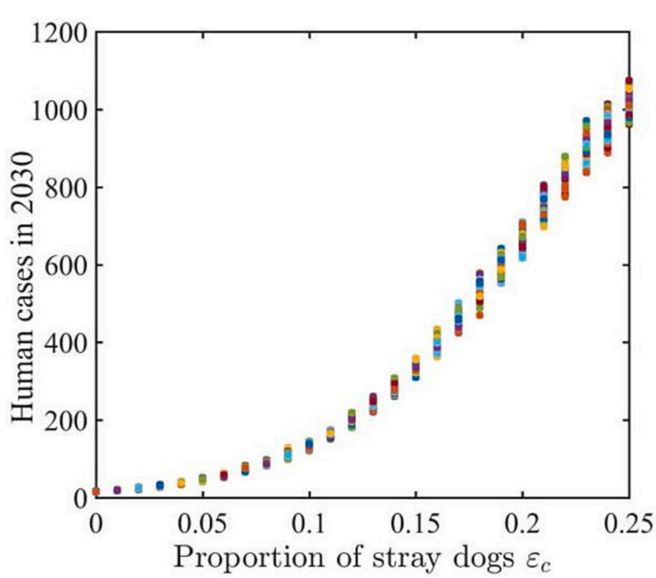

Fig. 8. The relationship between the proportion of stray dogs and the theoretical number of human cases in 2030.

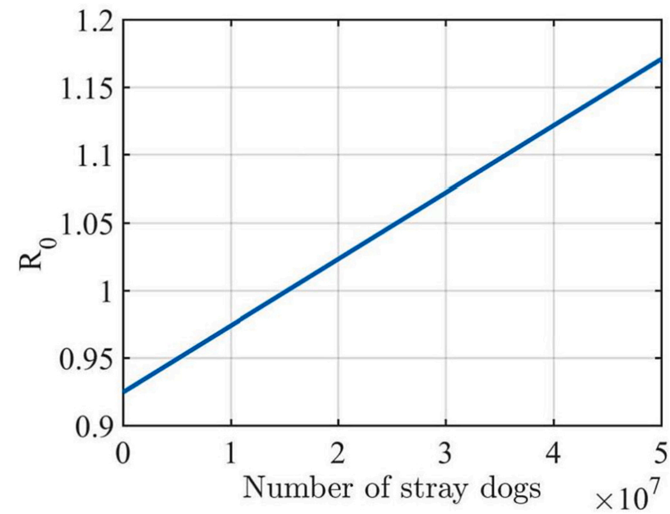

Fig. 9. R_0 in term of the number of stray dogs.

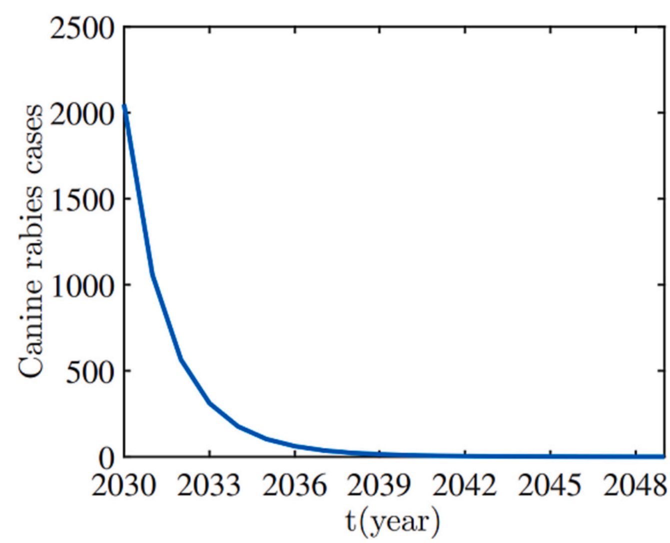

Fig. 10. The theoretical number of canine cases. The initial values of model variables are taken as follows. $S(0) = 1.2922 \times 10^8, E(0) = 1.9609 \times 10^3$, $I(0) = 96.1098, R(0) = 9.9276 \times 10^7, S_1(0) = 1.4517 \times 10^9$, $E_1(0) = 0.26$, $I_1(0) = 1.1434, R_1(0) = 8.5058 \times 10^6$.

When canine cases are eliminated, dogs may be bitten by infected wild animals to cause occurrence of rabies in human [40]. In order to prevent the occurrence of rebound phenomenon, the basic reproduction number must be less than 1 to ensure that rabies cannot spread among dogs. By observing the blue line in Fig. 11, we can obtain the necessary minimal immunization coverage rate with different number of dogs. When the number of dogs is 2.5284×10^8, the minimum immunization coverage of dogs needs to exceed 42%.

4. Discussion

Increasing immunization coverage rate and enhancing management of dogs should be combined to control the spread of rabies. The immunization coverage rate of urban and rural domestic dogs are very different, with higher immunization coverage rate in urban domestic dogs. And stray dogs are generally unvaccinated. Both the number and

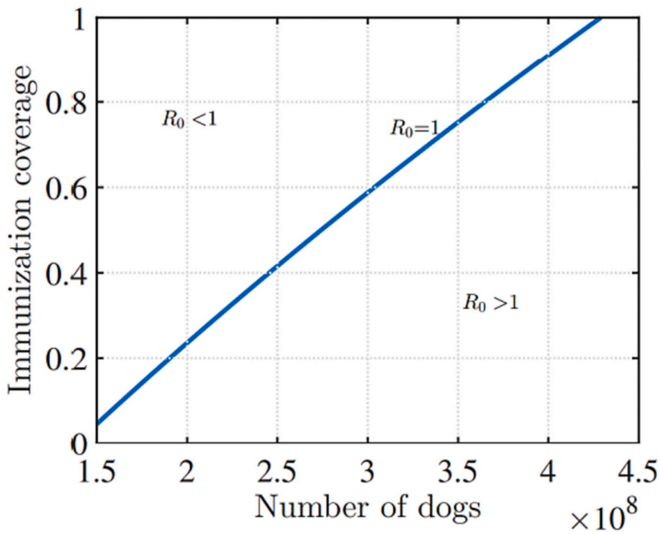

Fig. 11. Dog immunization coverage in terms of number of dogs. The blue line is where $R_0 = 1$. Above the blue line is where $R_0 < 1$, and below the blue line is where $R_0 > 1$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

vaccination rate of each type of dog can affect the overall canine immunization coverage, which in turn affects the number of human cases in 2030. So we discuss the impact of the number and immunization coverage of each type of dogs on human cases in 2030. Let $k = \varepsilon_a k_a + \varepsilon_b k_b + \varepsilon_c k_c$, where k_a, k_b and k_c are the immunization coverage rate of urban pet dogs, rural domestic dogs and stray dogs respectively; $\varepsilon_a, \varepsilon_b$ and ε_c are the proportion of pet dogs, rural domestic dogs and stray dogs respectively. Stray dogs are generally not vaccinated, so $k_c = 0$.

At present, the ratio of urban pet dogs, domestic dogs and stray dogs is 0.25:0.5:0.25. As shown in Table 2(a), if the immunization coverage rate of urban pet dogs reaches above 70% and the immunization coverage of rural domestic dog reaches above 60%, it can make human cases down to zero by 2030. From Table 2(b), when the ratio of urban pet dogs, rural domestic dogs, stray dogs is 0.35:0.4:0.25, the minimum immunization coverage of urban pet dogs should reach 70% and the minimum immunization coverage of rural domestic dog should reach 55%. If the number of stray dogs can be reduced through dog management, when the ratio of urban pet dogs, rural domestic dogs, stray dogs is 0.35:0.5:0.15, see Table 2(c), the minimum immunization coverage rate of urban pet dogs should reach 70% and the minimum immunization coverage rate of rural domestic dog should reach 45%. If stray dogs are adopted and rural domestic dogs are reduced with urbanization, the pressure of immunity of rural domestic dogs will be appropriately reduced.

From Table 2, we can see that under the same immunization

Table 2
Theoretical human cases in 2030 with different dog population size and different immunization coverage rate.

(a) $\varepsilon_a = 0.25, \varepsilon_b = 0.5, \varepsilon_c = 0.25$.

k_b / $I(2030)$ / k_a	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5	0.55	0.6
0.7	818	524	280	133	59	25	10	4	2	1	0
0.75	663	401	194	89	37	16	7	3	1	1	0
0.8	531	280	133	59	24	10	4	2	1	0	0
0.85	390	198	88	38	16	7	3	1	1	0	0
0.9	287	135	59	24	10	4	2	1	0	0	0
0.95	195	87	39	16	7	3	1	0	0	0	0
1	133	57	25	10	4	2	1	0	0	0	0

(b) $\varepsilon_a = 0.35, \varepsilon_b = 0.4, \varepsilon_c = 0.25$.

k_b / $I(2030)$ / k_a	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5	0.55	0.6
0.7	241	113	58	29	14	7	4	2	1	0	0
0.75	122	62	31	16	8	4	2	1	1	0	0
0.8	69	35	18	8	4	2	1	1	0	0	0
0.85	38	19	9	5	2	1	1	0	0	0	0
0.9	20	10	5	2	1	0	0	0	0	0	0
0.95	11	6	3	1	1	0	0	0	0	0	0
1	6	3	2	1	0	0	0	0	0	0	0

(c) $\varepsilon_a = 0.35, \varepsilon_b = 0.5, \varepsilon_c = 0.15$.

k_b / $I(2030)$ / k_a	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5	0.55	0.6
0.7	157	69	29	12	5	2	1	0	0	0	0
0.75	88	38	16	7	3	1	1	0	0	0	0
0.8	49	20	8	4	2	1	0	0	0	0	0
0.85	26	11	5	2	1	0	0	0	0	0	0
0.9	14	6	3	1	0	0	0	0	0	0	0
0.95	8	3	1	1	0	0	0	0	0	0	0
1	4	2	1	0	0	0	0	0	0	0	0

conditions, the smaller the number of stray dogs, the smaller the number of human cases in 2030. So reducing the proportion of stray dogs can greatly reduce the number of human cases in 2030. In addition, reducing the number of stray dogs can reduce the minimum immunization coverage rate required to eliminate rabies.

The culling of stray dogs can only temporarily reduce the number of stray dogs. Since their breeding rate is high and the population is growing rapidly, the culling of stray dogs cannot solve the problem fundamentally. In fact, it is found from the control of rabies within cities or across countries such as Ecuador, Indonesia and Bangladesh that large-scale dog culling has limit impact on the prevention and control of rabies in the long run [41].

In the long run, the ways to reduce the number of stray dogs are give as follows:

1. Setting up stray dog shelters and holding adoption activities
2. Carrying out stray dog neutering program. Neutering is one of the most effective ways to control the number of stray dogs and prevent their infinite reproduction, which can gradually reduce the number of stray dogs, so that dog immunization coverage rate is also easy to achieve and maintain.
3. Regulating the behavior of dog owners and enhancing public awareness. The government should call on people not to abandon dogs and strictly control dog's behavior, such as walking a dog on a leash.

5. Conclusion

In the last 8 years, China has made remarkable progress in the prevention and control of rabies and actively responded to the call of the World Health Organization (WH0) to eliminate dog-induced human rabies by 2030. By applying the dynamical model, this paper answers four questions: Whether the elimination goal can be achieved with current prevention and control efforts? If cannot, how much effort should be taken to achieve the elimination goal? How long will it take to eliminate rabies among dogs after eliminating human cases? How to maintain it after achieving the elimination goal for human and dog?

In this paper, based on the number of rabies cases from 2015 to 2022, with the help of dynamical model, we predict that human rabies cases will increase again and reach another peak in 2033, and finally become stable, which is consistent with the prediction in Zhang's paper [1]. And, we find that it is difficult to achieve the goal of eliminating dog-induced human rabies cases by 2030 with current intensity of measures. Through carrying out numerical simulation, when average immunization coverage of dogs is increased to 47% from now on, the goal of human cases will be achieved. Moreover, we give the minimal immunization coverage for each kind of dogs. According to the current transmission rate and the proportion of the number of dogs, when the immunization coverage of urban pet dogs is 70%, the immunization coverage of rural domestic dogs must be increased to 60%. If stray dogs are adopted and rural domestic dogs are reduced with urbanization, the pressure of immunity of rural domestic dogs will be appropriately reduced. Controlling the number of dogs, especially stray dogs, is an important step in controlling the spread of rabies. However, large-scale dog culling has limit impact on the prevention and control of rabies in the long run. Humane tools of dog population management, such as sterilization, can effectively reduce the number and size of dogs, and make it easier to improve the whole immunization coverage rate of dogs. The government should take measures to control the number of stray dogs below 15.27 million. After achieving the goal, 47% immunization coverage of dogs need to be maintained for next 18 years to eliminate canine cases. After both human and canine cases are eliminated, the minimal immunization coverage rate of dogs can be reduced appropriately.

To prevent the spread of wild rabid animals to dogs and the rebound of rabies after eliminating dog rabies cases, we must promise whole immunization coverage rate of dogs above 42% and the immunization coverage of urban pet dogs and rural domestic dogs above 70% and 50%, respectively, and the number of stray dogs should be reduced.

In addition, the prevention and control measures of rabies should be strengthened: the detection of rabies in animals, including wild animals; immunization for dogs and post-exposure prophylaxis for humans; the management of dogs, especially free-range dogs and stray dogs. The government should publicize the knowledge of rabies prevention and control, requires people to take action to protect animals, not to abandon domestic dogs, to vaccinate dogs in time and adopt stray dogs.

Since there is no official and detailed record of the number of dogs, this paper only provides a rough estimate of the number of dogs, which is bound to have some errors. In future research, we will establish a coupled dynamical model to study the changes of urban pet dogs population, rural domestic dogs population, and stray dogs population, respectively.

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CRediT authorship contribution statement

Miao-Miao Lv: Writing – original draft, Data curation, Formal analysis, Visualization, Methodology, Software. **Xiang-Dong Sun:** Writing – review & editing, Validation, Supervision. **Zhen Jin:** Methodology, Supervision, Writing-review & editing. **Hai-Rong Wu:** Writing – review & editing, Validation. **Ming-Tao Li:** Writing – review & editing, Formal analysis, Methodology, Software. **Gui-Quan Sun:** Writing – original draft, Formal analysis, Methodology. **Xin Pei:** Formal analysis, Data curation. **Yu-Tong Wu:** Validation, Supervision. **Ping Liu:** Validation, Supervision. **Li Li:** Formal analysis, Supervision. **Juan Zhang:** Writing – review & editing, Data curation, Formal analysis, Visualization, Methodology, Software.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

The data can be obtained from manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.onehlt.2023.100615.

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