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Christopher Turner

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# An Application of Differential Mathematical Modeling Techniques to Study the Ongoing Rabies Epizootic in China

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An Application of Differential Mathematical Modeling Techniques to Study the  
Ongoing Rabies Epizootic in China

by

Christopher Turner, B.S., M.S.

Presented to the Faculty of the Graduate School of

Stephen F. Austin State University

In Partial Fulfillment

of the Requirements

For the Degree of

Master of Natural and Applied Sciences

STEPHEN F. AUSTIN STATE UNIVERSITY

May 2022

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Ongoing Rabies Epizootic in China

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Christopher Turner, B.S., M.S.

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## **ABSTRACT**

Rabies remains a global public health issue with a wide variety of neurological symptoms such as confusion, slight paralysis, hypersalivation, and hydrophobia. Rabies is usually fatal once symptoms appear. Many species are reservoirs for rabies, such as foxes, racoons, and wild dogs, which in turn can transmit the disease to humans, leading to complex transmission chains. There is a long latent period of rabies, between 1 to 3 months after infection, which further complicates control efforts. Mathematical modeling is a valuable tool in the study of infectious disease outbreaks and there have been many models applied to rabies outbreaks. However, these focus on localized outbreaks that usually involve a single lineage and there have been fewer studies that attempt to model a rabies outbreak at the national level. In this work, we will investigate the surveillance data collected by the Chinese Center for Disease Control for the current Rabies epizootic in China that involves a displacement of one rabies lineage with another. This paper will investigate the suitability of different models for capturing the observed case data at the provincial level.

## CONTENTS

<b>ABSTRACT</b> . . . . .	iii
<b>1 HISTORY OF RABIES</b>	<b>1</b>
1.1 Motivation . . . . .	1
1.2 Rabies Prevention . . . . .	1
1.3 History of Rabies in China . . . . .	2
1.4 Different Rabies Lineages Currently Found in China . . . . .	4
1.5 The Chinese CDC Data used in this study . . . . .	4
<b>2 SIR MODELING</b>	<b>7</b>
2.1 The Basic SIR Model . . . . .	7
2.2 Simple SIR Model . . . . .	8
2.3 SIR Model with Vital Dynamics . . . . .	8
2.4 Two Group SIR Model . . . . .	9
<b>3 MODELING RABIES IN CHINA</b>	<b>10</b>
3.1 Simple SIR Model . . . . .	10
3.2 Human-Dog Hybrid SIR model . . . . .	14
<b>4 DISCUSSION AND CONCLUSION</b>	<b>20</b>
4.1 Conclusion . . . . .	20
4.2 Future Work . . . . .	21
<b>APPENDIX A</b> . . . . .	<b>23</b>
<b>APPENDIX B</b> . . . . .	<b>26</b>
<b>BIBLIOGRAPHY</b> . . . . .	<b>28</b>
<b>VITA</b> . . . . .	<b>31</b>

## LIST OF TABLES

4.1 Confirmed Rabies Cases 1996-2020 . . . . .	24
4.2 Population in China 1996-2019 . . . . .	25

## LIST OF FIGURES

1.1 Annual Number of Rabies Cases in China from 1949 - 2020 . . . . .	2
1.2 The Third Epizootic Wave of Rabies in China . . . . .	3
1.3 Cumulative Rabies Cases in China from 1996-2020 . . . . .	5
1.4 Cumulative Rabies Cases in China from 1996-2020 . . . . .	5
3.1 The Infection Curve for Guangdong . . . . .	11
3.2 The Infection Curve for Guangxi . . . . .	11
3.3 The Infection Curve for Guizhou . . . . .	11
3.4 The Infection Curve for Hunan . . . . .	11
3.5 The Infection Curve for Sichuan . . . . .	12
3.6 The Infection Curve for Fujian . . . . .	12
3.7 The Infection Curve for Jiangxi . . . . .	13
3.8 The Infection Curve for Hubei . . . . .	13
3.9 The Infection Curve for Chongqing . . . . .	14
3.10 The Infection Curve for Yunnan . . . . .	14
3.11 The Infection Curve for Yunnan using the Human-Dog Hybrid Model	16
3.12 The Infection Curve for Yunnan (Simple SIR Model). Infection rate is 189 people per year. . . . .	17
3.13 The Infection Curve for Yunnan (Human-Dog Hybrid Model). In- fection rate is 33 people per year. . . . .	17
3.14 The Infection Curve for Guangxi using the Human-Dog Hybrid Model	17
3.15 The Infection Curve for Guangxi (Simple SIR Model) . . . . .	18
3.16 The Infection Curve for Guangxi (Human-Dog Hybrid Model) . . .	18
3.17 The Infection Curve for Guangdong (Simple SIR Model) . . . . .	18
3.18 The Infection Curve for Guangdong (Human-Dog Hybrid Model) .	18
3.19 The Infection Curve for Hunan (Simple SIR Model) . . . . .	19



3.20	The Infection Curve for Hunan (Human-Dog Hybrid Model)	. . .	19
3.21	The Infection Curve for Guizhou (Simple SIR Model)	. . . . .	19
3.22	The Infection Curve for Guizhou (Human-Dog Hybrid Model)	. . .	19
4.1	The Infection Curve for Jiangsu.	$\beta = 221.09 \pm 9.00$ $\alpha = 220.66 \pm 9.00$	26
4.2	The Infection Curve for Henan.	$\beta = 264.67 \pm 0.14$ $\alpha = 264.18 \pm 0.14$	26
4.3	The Infection Curve for Anhui.	$\beta = 337.75 \pm 0.14$ $\alpha = 336.96 \pm .13$	26
4.4	The Infection Curve for Hebei.	$\beta = 171.95 \pm 8.40$ $\alpha = 171.67 \pm 8.39$	26
4.5	The Infection Curve for Zhejiang.	$\beta = 230.84 \pm 10.72$ $\alpha = 230.55 \pm$ 10.70 . . . . .	27
4.6	The Infection Curve for Hebei.	$\beta = 94.75 \pm 6.36$ $\alpha = 94.42 \pm 6.35$ .	27
4.7	The Infection Curve for Shanxi.	$\beta = 192.87 \pm 11.62$ $\alpha = 192.54 \pm$ 11.60 . . . . .	27
4.8	The Infection Curve for Tianjin.	$\beta = 444.22 \pm .16$ $\alpha = 443.66 \pm .16$	27
4.9	The Infection Curve for Shandong.	$\beta = 294.86 \pm 9.17$ $\alpha = 294.39 \pm$ 9.16 . . . . .	27
4.10	The Infection Curve for Shaanxi.	$\beta = 161.36 \pm 9.96$ $\alpha = 161.18 \pm 9.94$	27

# 1 HISTORY OF RABIES

## 1.1 Motivation

Rabies is a global problem, but is particularly acute in Asia and Africa. According to the World Health Organization (WHO), the total number of human deaths globally due to dog-mediated rabies is estimated to be around 59,000 annually. These numbers seem small in comparison to other infectious diseases, however a large proportion of these deaths occur in children [1], [20]. Over 95% of rabies victims are reported in Asia and Africa and nearly all of these victims are due to rabid dog bites [1], [20]. Rabies and the symptoms should not be ignored, but it seems that it is being neglected in developing parts of the world, particularly in rural areas [1], [20]. Rabies is often under reported, due to either no organized control or surveillance for proper data collection, or due to misdiagnosis in patients [12]. These issues have lead to individuals and countries having to use various mathematical modeling techniques to estimate many different facets of these outbreaks.

## 1.2 Rabies Prevention

There are many different ways to eliminate or eradicate rabies globally. The best way to eliminate rabies is in vaccination. Rabies is vaccine preventable and vaccination is the most cost effective strategy to eliminating rabies [1]. Rabies has been effectively under control in North America and Europe due to the introduction of both more potent vaccines for domesticated animals and a rabies vaccine that is contained in bait for free ranging wildlife populations [2]. Another way to help eliminate rabies is in the education of people on dog behavior and bite prevention, which can lead to a decrease in incidence of human rabies [1]. A third option to help eliminate rabies, which is usually used after a suspected bite has occurred, is immunization after an exposure (post-exposure prophylaxis or PEP) [1]. Pre-exposure immunization is also recommended for those in high exposure risk areas. One option that is often overlooked is surveillance. The Covid-19 pandemic has highlighted the importance of comprehensive surveillance data to track the progress of a novel disease outbreak, and it has also exposed the limitations that arise by incomplete information. There is no global surveillance data for rabies, but China has attempted to track cases since the formation of the People's Republic of China in 1949 and the annual human case data is available at the provincial level.

### 1.3 History of Rabies in China

Rabies was first reported in China in 556 B.C. and subsequently reported for the next 2500 years [10]. As mentioned in section 1.2, China has been tracking human rabies case since 1949. This surveillance data reveals three epizootic waves. Figure 1.1 illustrates the general trend in rabies found in China from 1949 to 2020.

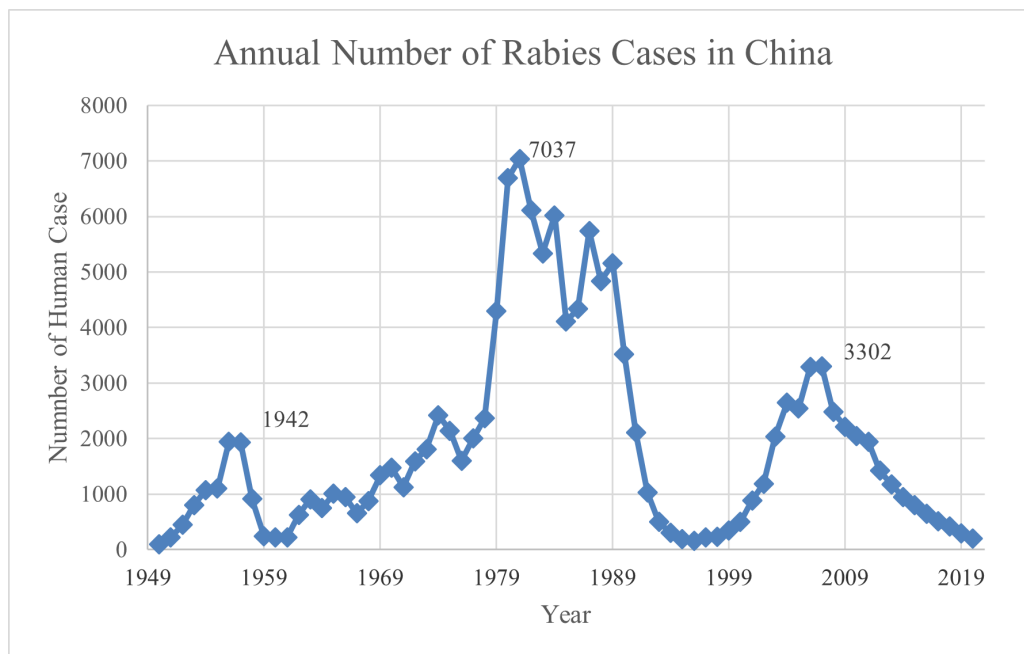
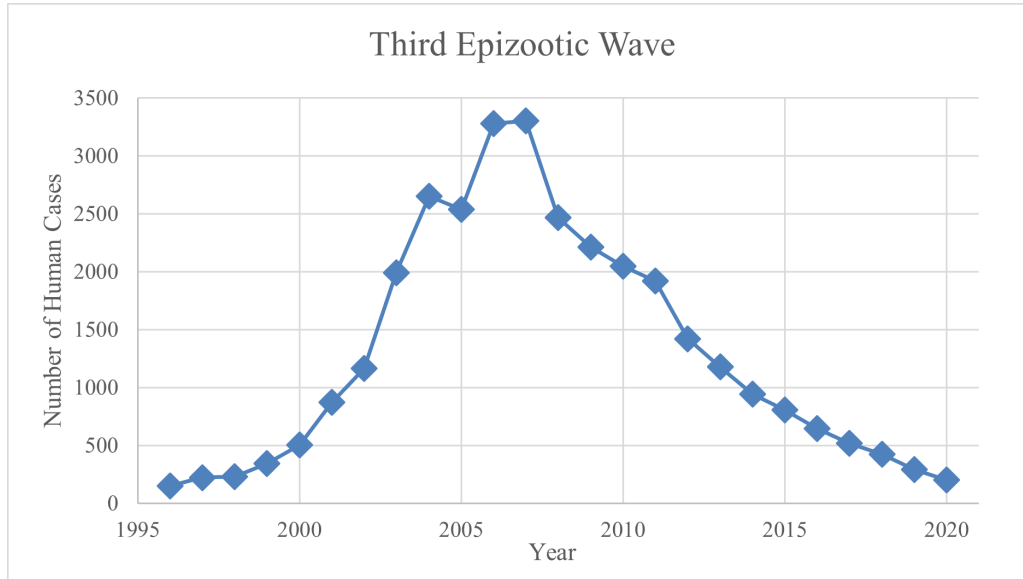


Figure 1.1: Annual Number of Rabies Cases in China from 1949 - 2020

As can be seen in Figure 1.1, there are 3 epizootic waves during this time period. The first epizootic wave was between 1949 and 1959, with the highest number of cases in that time being 1,942 cases in 1956. The second epizootic wave was between around 1962 and 1993 with the highest number of cases in that time being 7,037 cases in 1981. After this second epizootic wave, in 1985, a national rabies control and prevention program was implemented and by 1996 rabies cases had decreased to 159 cases [3]. However, after this point in time, the number of cases started to rise rapidly and the third epizootic wave began. This third epizootic wave, and the one of interest in this paper, was between 1996 and 2020 with a peak of 3302 cases in 2007. Figure 1.2 is the general trend in rabies during this third epizootic wave.



**Figure 1.2:** The Third Epizootic Wave of Rabies in China

During the third epizootic wave, a national rabies surveillance program (China National Statutory Notifiable Communicable Disease Reporting System) was implemented in 2005 in provinces and cities with the highest infection rates [14]. The goals of this program include identifying factors driving the epidemic, the populations most at risk, and the effectiveness of control measures. As part of the surveillance program, samples were collected from local areas where a suspected rabies outbreak occurred and a portion of these samples were selected for sequencing of the viral genome. From this sequencing, it was shown that there were six primary lineages or strains, with the China I and China II lineages being the most predominant. It was also shown that the China II lineage was the dominant strain of rabies during the second epizootic wave, but the China I lineage was gradually replaced by the China II lineage in the third epizootic wave [16], [3]. In China, domestic dogs are the main source of rabies along with wildlife, such as the ferret badger, also playing an undetermined role in the endemic [9]. Bats may play a role in rabies infection, but the impact on this epizootic wave has not been investigated [6]. These factors lead to difficulty in controlling rabies in China. Based on surveillance data and epidemiological surveys done during this time period, new regulations on rabies control was drafted by the Ministry of Agriculture and Health in China. These regulations focused on vaccination of domestic animals, especially in rural areas, which proved effective [21].

The goals of this study were to model the lineage displacement of the China II strain by the China I strain using the surveillance data, and to see if there were statistically significant differences between the estimated model parameters that could

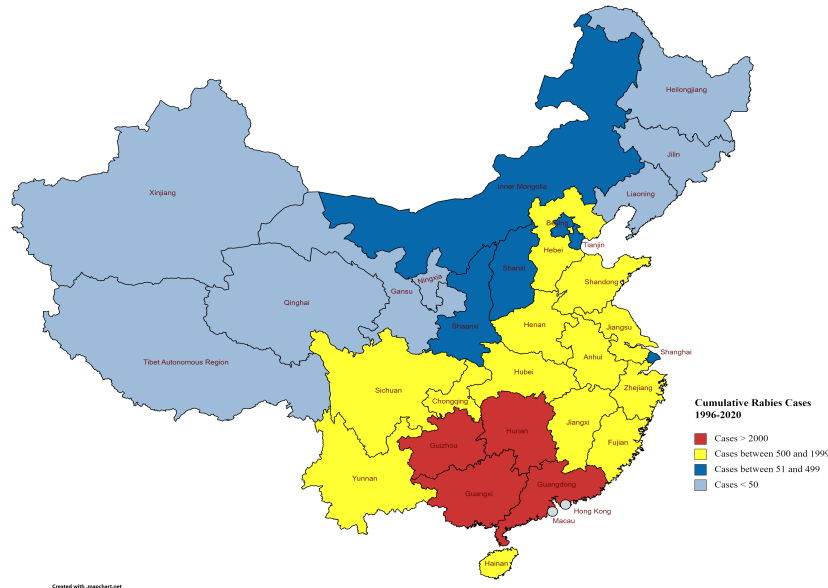
possibly explain the improved fitness of China I.

## 1.4 Different Rabies Lineages Currently Found in China

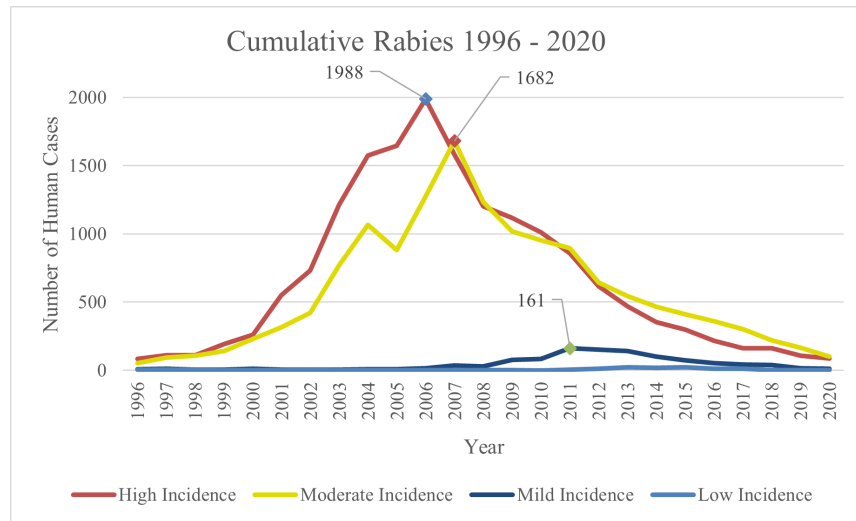
Previous phylogenetic investigation of the sequences from viral isolates collected in China identify six major lineages, China I to China VI, with strong support [16]. Investigation of the relationships among these lineages identify the current epizootic to be associated with China I and China II, with the remaining lineages circulating in wildlife with sporadic spillover into the dog population. Moreover, it was identified that China II was the major lineage circulating in the previous epizootic, but China I was gradually displacing China II as the dominant strain in the current epizootic. More recently, a new lineage, China VII was identified as being imported from Nepal [15].

## 1.5 The Chinese CDC Data used in this study

Before we begin discussion about the various differential models we will be using, we should discuss the data that has been provided. China has 31 provinces and municipalities. Using the information found in Table 5.1 in Appendix A, we have the number of confirmed deaths due to rabies for each province from 1996 to 2020. This data was provided by the Chinese Center for Disease Control (China CDC). The data in Table 5.2 is the total human population for each province from 1996 to 2019. Using the infection data provided, Figure 1.3 is a preliminary “heat” map of the rabies infection in China during this time period. From this we see that a majority of the rabies infections during this time period are in the southern region of China and then spread outward from there. From this map, we see that we have regions with high (cases greater than 2000) incidence of rabies during this time period, along with regions with moderate (between 500 and 1999 cases), mild (between 51 and 499 cases) and low (less than 50 cases) incidence. Figure 1.4 shows the general trend in these four areas. Figure 1.4 is the same as Figure 1.2, but we have broken it up into these four incidence regions. From Figure 1.4, we can see that in the high incidence regions, they reached the maximum number of cases in 2006 with 1988 cases, but the moderate incidence regions did not reach its peak until 2007 with 1682 cases. Also of note, the mild incidence regions reached a peak much later in 2011 with a total number of cases at 161. This is what lead to the discussion of whether the rabies cases are all of the same lineage [16].



**Figure 1.3:** Cumulative Rabies Cases in China from 1996-2020



**Figure 1.4:** Cumulative Rabies Cases in China from 1996-2020

From this data, we will begin modeling the rabies endemic from 1996 to 2019 for most of these provinces. However, one should note that for 1996, there are a few provinces with no confirmed rabies infections, so we have to adjust our start year for those provinces. One should also note that our population data includes cities themselves and some other provinces that we have no infection data for, in which case we have excluded these from the analysis. Finally, as discussed in section 1.4,

these cumulative cases are a combination of cases occurring from the China I and China II lineages.

There are many different epidemic modeling approaches using SIR, such as modeling the spatial/temporal components of rabies [11] or modeling the control mechanisms to prevent the spread of the rabies virus [13] or modeling how to reduce the impact once the disease has become epidemic [18] or using a Monte Carlo simulation to estimate the number of infectious dogs in a province [17]. The next section will discuss some of the ways to model an epidemic using various SIR modeling.

## 2 SIR MODELING

### 2.1 The Basic SIR Model

A tried and true method for modeling epidemiological outbreaks is the Susceptible, Infected, and Recovered model (SIR), first introduced in 1927 by Kermack and McKendrick to study the plague and cholera epidemics in London and Bombay (Mumbai), respectively [8]. The model is as follows,

$$\frac{dS}{dt} = -\beta SI \tag{2.1}$$

$$\frac{dI}{dt} = \beta SI - \alpha I \tag{2.2}$$

$$\frac{dR}{dt} = \alpha I \tag{2.3}$$

where  $S$  is the proportion of susceptible individuals per total population,  $I$  is the proportion of infected individuals per total population,  $R$  is the proportion of individuals that have recovered from the infection per total population,  $\beta$  is the average infection rate for the disease, and  $\alpha$  is the average rate of recovery from infection.

There are several key assumptions in use with this model. The first assumption is that there is an equal probability for each individual to contract the disease. The second and third assumptions are that the number of individuals leaving the susceptible population must be the same number of individuals that are entering the infected population, along with the number of individuals that are leaving the infected population must be the same as the number of individuals entering the recovered population. This process which is occurring simultaneously is often referred to as the Law of Mass Action. The final assumption in this model is that the rate of infection and the rate of recovery is much faster than the birth and death rates. These assumptions will hold for all of the proceeding models, unless otherwise noted. This model has been used to model other epidemics as well, such as when modeling a flu outbreak in a British boarding school [7].



## 2.2 Simple SIR Model

Now one could also rewrite equations (3.1) – (3.3) to account for the total population in the calculations, as found in the 2000 SIAM Review [5]. This model is

$$\frac{dS}{dt} = -\frac{\beta SI}{N} \quad (2.4)$$

$$\frac{dI}{dt} = \frac{\beta SI}{N} - \alpha I \quad (2.5)$$

$$\frac{dR}{dt} = \alpha I \quad (2.6)$$

where  $S$  is the number of susceptible individuals,  $I$  is the number of infected individuals,  $R$  is the number of individuals that have recovered from the infection,  $\beta$  is the infection rate for the disease,  $\alpha$  is the rate of recovery from infection, and  $N = S + I + R$ , which is used to encapsulate the total population.

This model is the same as the basic SIR model, just removing the proportionality in the  $S, I, R$  terms. We can consider the term  $N$  as proportionality constant. It is useful to help prevent the population from reaching a critical mass, which would not be sustainable in real world applications. One could also think of this term as a sort of carrying capacity.

## 2.3 SIR Model with Vital Dynamics

A variation of equations (3.4) – (3.6) is one where we include a birth rate, along with a natural death rate in the population. This model, usually described as an SIR model with vital dynamics or demography, which can be found in Modeling Infectious Diseases in Humans and Animals [7] is as follows

$$\frac{dS}{dt} = \Lambda - \mu S - \frac{\beta SI}{N} \quad (2.7)$$

$$\frac{dI}{dt} = \frac{\beta SI}{N} - \alpha I - \mu I \quad (2.8)$$

$$\frac{dR}{dt} = \alpha I - \mu R \quad (2.9)$$

where  $S, I, R, N, \beta$ , and  $\alpha$  are the same as above. We let  $1/\Lambda$  be the "lifespan" of the individual, which then leads to  $\Lambda$  being the number of new susceptible individuals added to the population, and  $\mu$  is the natural death rate. This model has been used to study measles in New York City from 1891 to 1984 [4].

## 2.4 Two Group SIR Model

Expanding on equations (3.7) – (3.9), we can talk about an infectious disease that can move between two groups, A and B. A simple version of this model, found in Modeling Infectious Diseases in Humans and Animals [7] is as follows

$$\frac{dS_A}{dt} = \Lambda_A - \mu_A S_A - \frac{\beta_{AB} S_A I_B}{N} - \frac{\beta_{AA} S_A I_A}{N} \quad (2.10)$$

$$\frac{dI_A}{dt} = \frac{\beta_{AB} S_A I_B}{N} + \frac{\beta_{AA} S_A I_A}{N} - \alpha_A I_A - \mu_A I_A \quad (2.11)$$

$$\frac{dR_A}{dt} = \alpha_A I_A - \mu_A R_A \quad (2.12)$$

$$\frac{dS_B}{dt} = \Lambda_B - \mu_B S_B - \frac{\beta_{BA} S_B I_A}{N} - \frac{\beta_{BB} S_B I_B}{N} \quad (2.13)$$

$$\frac{dI_B}{dt} = \frac{\beta_{BA} S_B I_A}{N} + \frac{\beta_{BB} S_B I_B}{N} - \alpha_B I_B - \mu_B I_B \quad (2.14)$$

$$\frac{dR_B}{dt} = \alpha_B I_B - \mu_B R_B \quad (2.15)$$

where  $S_A$  is the number of susceptible individuals from group A,  $I_A$  is the number of infected individuals from group A, and  $R_A$  is the number recovered individuals from group A. Similarly,  $S_B$  is the number of susceptible individuals from group B,  $I_B$  is the number of infected individuals from group B, and  $R_B$  is the number of recovered individuals from group B. Note that  $N = S_A + I_A + R_A + S_B + I_B + R_B$ . Now  $\beta_{AB}$  is the infection rate for the disease when an individual from group A interacts with an individual from group B,  $\beta_{AA}$  is the infection rate for the disease when an individual from group A interacts with another member of group A,  $\beta_{BA}$  is the infection rate for the disease when an individual from group B interacts with an individual from group A,  $\beta_{BB}$  is the infection rate for the disease when an individual from group B interacts with another member of group B,  $\alpha_A$  is the recovery rate for individuals in group A,  $\alpha_B$  is the recovery rate for individuals in group B,  $\Lambda_A$  is the number individuals from group A added per time step,  $\Lambda_B$  is the number individuals from group B added per time step,  $\mu_A$  is the natural death rate for group A, and  $\mu_B$  is natural death rate for group B.

As one can see, there are many different variations of the SIR model one can use to approximate the spread of a disease. These models can get more complex as needed with relative ease. The next section will elaborate on the two different SIR differential models used to estimate the infection rate using the data provided.

### 3 MODELING RABIES IN CHINA

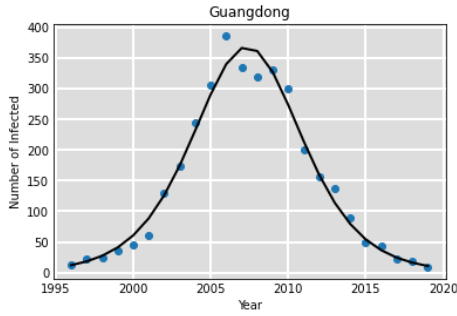
#### 3.1 Simple SIR Model

As noted in the first section, the only information that we have been provided is the number of confirmed infections due to rabies and the total population for each province. Using a simple SIR model, like the ones in equations (3.4) – (3.6), we make an initial, relatively simple model of the infections in each province. We should note here that we have made the assumption that each province is self contained, as in people do not leave from one province to another. From this, we have the following SIR model

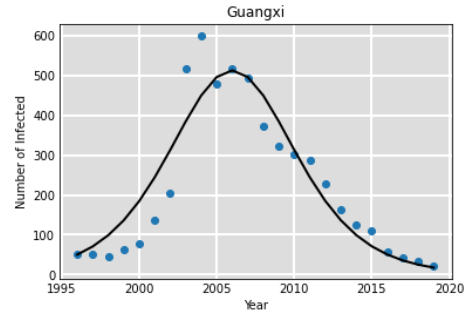
$$\begin{aligned}\frac{dS}{dt} &= -\frac{\beta SI}{N} \\ \frac{dI}{dt} &= \frac{\beta SI}{N} - \alpha I \\ \frac{dR}{dt} &= \alpha I\end{aligned}$$

where  $S$  is the number of susceptible humans in a given province, or rather those that have not been infected with rabies,  $I$  is the number of rabies infected humans in a given province,  $R$  is the number of humans who have “recovered” from rabies in a given province,  $\beta$  is the average infection rate for rabies per year in that province, and  $\alpha$  is the average “recovery” rate for rabies per year in that province, and  $N = S + I + R$ , which is the total number of humans in the province. The recovery rate is in quotations here due to the fact that there is no actual recovery for rabies, the individuals are simply no longer able to move back into the susceptible population. This “recovery” rate is closer to a death rate due to a rabies infection per year in a given province.

The following figures are the infection curves found using this SIR model, along with the estimates for the average infection rate per year and the average recovery rate per year. One should note that the errors associated with each of the parameter estimates are standard errors, not standard deviations. Using the ordinary differential integrator found in the `scipy` package in python we have the following figures for the high incidence provinces.

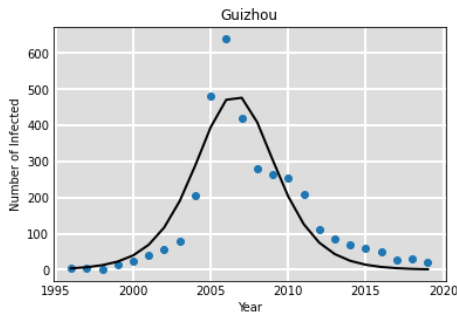


**Figure 3.1:** The Infection Curve for Guangdong

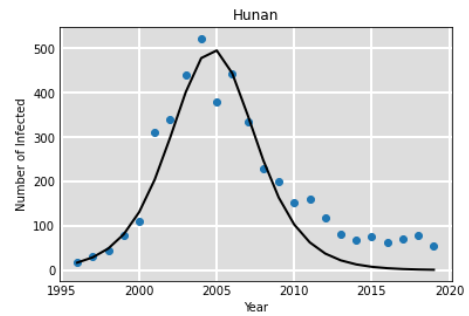


**Figure 3.2:** The Infection Curve for Guangxi

Figure 3.1 and 3.2 are the infection curves for the provinces of Guangdong and Guangxi, respectively. From the fit found in Figure 3.1, we have the average infection rate for the province of Guangdong is  $150.74 (\pm 1.64)$ , with an average death rate of  $150.33 (\pm 1.64)$ . This means that the average number of people infected per year in Guangdong is about 151 people and the average number of deaths due to rabies per year in Guangdong is about 151 people. From the fit found in Figure 3.2, we have the average infection rate for the province of Guangxi is  $78.95 (\pm 2.12)$ , with an average death rate of  $78.60 (\pm 2.11)$ . This means that the average number of people infected per year in Guangxi is about 79 people and the average number of deaths due to rabies per year in Guangdong is about 79 people.



**Figure 3.3:** The Infection Curve for Guizhou

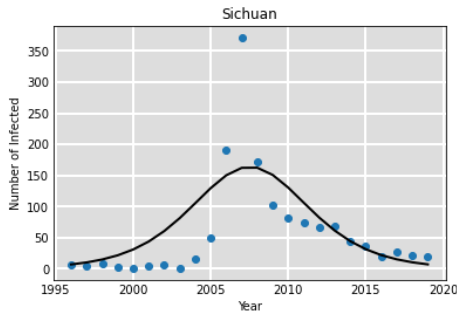


**Figure 3.4:** The Infection Curve for Hunan

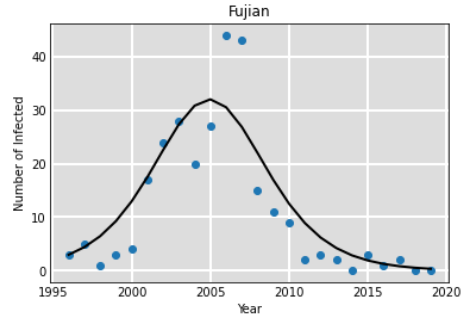
Figure 3.3 and 3.4 are the infection curves for the provinces of Guizhou and Hunan, respectively. From the fit found in Figure 3.3, we have the average infection rate for the province of Guizhou is  $113.67 (\pm 3.78)$ , with an average death rate of  $113.08 (\pm 3.77)$ . This means that the average number of people infected per year in Guizhou is about 114 people and the average number of deaths due to rabies per year in Guizhou is about 114 people. From the fit found in Figure 3.4, we have the average infection rate for the province of Hunan is  $139.85 (\pm 4.12)$ , with an average death rate of  $139.32 (\pm 4.11)$ . This means that the average number of people infected per

year in Hunan is about 140 people and the average number of deaths due to rabies per year in Hunan is about 140 people.

Looking at some of the provinces that had moderate incidence cases, we see that the goodness of fit is not near as good as the previous figures.



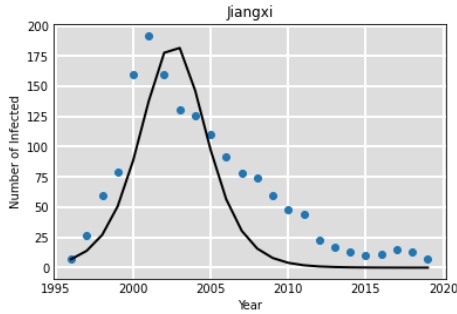
**Figure 3.5:** The Infection Curve for Sichuan



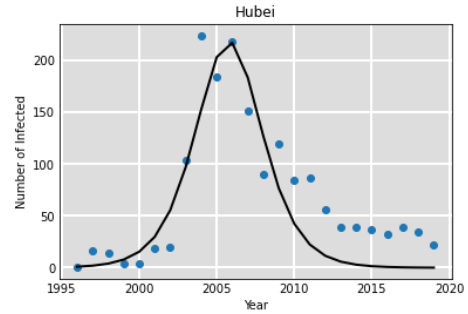
**Figure 3.6:** The Infection Curve for Fujian

Figure 3.5 and 3.6 are the infection curves for the provinces of Sichuan and Fujian, respectively. From the fit found in Figure 3.5, we have the average infection rate for the province of Sichuan is  $197.73 (\pm 15.29)$ , with an average death rate of  $197.34 (\pm 15.27)$ . This means that the average number of people infected per year in Sichuan is about 198 people and the average number of deaths due to rabies per year in Sichuan is about 198 people. From the fit found in Figure 3.6, we have the average infection rate for the province of Fujian is  $311.29 (\pm 12.48)$ , with an average death rate of  $310.90 (\pm 12.46)$ . This means that the average number of people infected per year in Fujian is about 312 people and the average number of deaths due to rabies per year in Fujian is about 311 people. Notice that Figure 3.5 seems to capture most of the data, except for the one spike of 372 case in 2007. Also the infection rate for Fujian is higher than the total number of cases. Further investigation is warranted to determine whether there was an actual two-fold increase in cases in one year Sichuan or if we have some type of under reporting happening during this time in Sichuan. We should also look more closely at the infection rate in Fujian and try to determine whether our assumptions are correct or if there is some other underlying issues.

Investigating some of the other provinces with moderate incidence cases, Figure 3.7 and 3.8 are the infection curves for Jiangxi and Hubei, respectively.



**Figure 3.7:** The Infection Curve for Jiangxi



**Figure 3.8:** The Infection Curve for Hubei

From the fit found in Figure 3.7, we have the average infection rate for the province of Jiangxi is  $242.48 (\pm 15.04)$ , with an average death rate of  $241.79 (\pm 15.00)$ . This means that the average number of people infected per year in Jiangxi is about 243 people and the average number of deaths due to rabies per year in Jiangxi is about 242 people. From the fit found in Figure 3.8, we have the average infection rate for the province of Hubei is  $253.64 (\pm 10.72)$ , with an average death rate of  $252.94 (\pm 10.71)$ . This means that the average number of people infected per year in Hubei is about 254 people and the average number of deaths due to rabies per year in Hubei is about 253 people. As we see, the average infection rate in Hubei was found to be 254 people per year, which is higher than the highest number of cases during this time period. This also leads to further investigation about whether there was under reporting during this time period, or whether we need to make some adjustments to our model.

As mentioned in Section 1.4, there are a few provinces that did not have a case of rabies until later during this epizootic wave. Two areas that fall under this criteria are Chongqing and Yunnan. Figures 3.9 and 3.10 are the infection curves for Chongqing and Yunnan, respectively.

From the fit found in Figure 3.9, we have the average infection rate for the municipality of Chongqing between 2004 and 2019 is found to be  $390.20 (\pm 27.39)$ , with an average death rate during this time period found to be  $388.77 (\pm 27.31)$ . This means that the average number of people infected per year in Chongqing is about 391 people and the average number of deaths due to rabies per year in Chongqing is about 389 people. These rates are so high due to the rapid nearly four fold increase between 2006 and 2007 and the subsequent decrease from 2008 to 2013. Further investigation is warranted for this province.

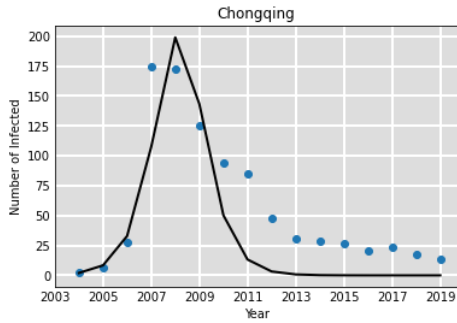


Figure 3.9: The Infection Curve for Chongqing

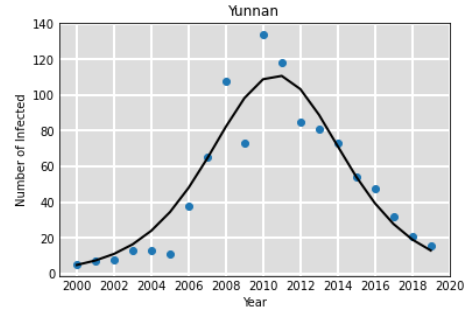


Figure 3.10: The Infection Curve for Yunnan

From the fit found in Figure 3.10, we have the average infection rate for the province of Yunnan between 2000 and 2019 is found to be  $189.54 (\pm 4.69)$ , with an average death rate during this time to be  $189.13 (\pm 4.68)$ . This means that the average number of people infected per year in Yunnan is about 190 people and the average number of deaths due to rabies per year in Yunnan is about 190 people. This also leads to further investigation. Appendix B has the available figures and estimates for the other provinces in China along with the github repository for the code used to determine both the models along with the fits.

From these few province examples, we see that we are running into issues with our parameter estimations, whether from incomplete/inaccurate data or our model assumptions are wrong. The next section will address a possible solution to our model assumptions.

### 3.2 Human-Dog Hybrid SIR model

In the previous subsection, we created a simple SIR model for rabies infections in each province. This model has a flaw in that it assumes that rabies is spread from human to human. However, this is not the case. Rabies in humans is predominately spread through animal bites and scratches. Our model does not capture this. We also know that the human and dog populations are not static. The time frame we are looking at spans 24 years, so it is safe to say that some humans and dogs were added and removed, naturally, from the population during this time. Including these vital dynamics, the following is a proposed human-dog hybrid SIR model, which is

a modification of equations (3.10) – (3.15).

$$\frac{dS_H}{dt} = \Lambda_H N_H - \mu_H S_H - \frac{\beta_{DH} S_H I_D}{N} \quad (3.1)$$

$$\frac{dI_H}{dt} = \frac{\beta_{DH} S_H I_D}{N} - \alpha_H I_H \quad (3.2)$$

$$\frac{dR_H}{dt} = \alpha_H I_H \quad (3.3)$$

$$\frac{dS_D}{dt} = \Lambda_D N_D - \mu_D S_D - \frac{\beta_D S_D I_D}{N_D} \quad (3.4)$$

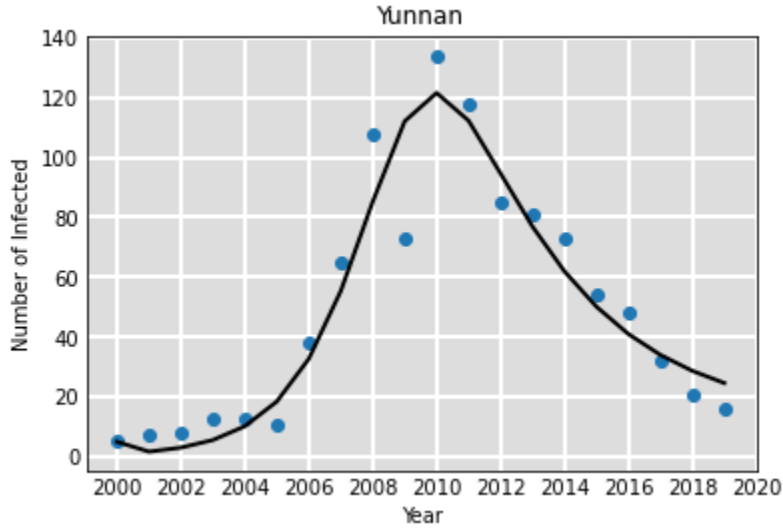
$$\frac{dI_D}{dt} = \frac{\beta_D S_D I_D}{N_D} - \alpha_D I_D \quad (3.5)$$

$$\frac{dR_D}{dt} = \alpha_D I_D \quad (3.6)$$

where  $S_H$  is the number of susceptible humans,  $I_H$  is the number of infected humans,  $R_H$  is the number recovered humans, or rather the number of human deaths due to rabies, and  $N_H = S_H + I_H + R_H$  is the total number of humans. Similarly,  $S_D$  is the number of susceptible dogs,  $I_D$  is the number of infected dogs,  $R_D$  is the number of recovered dogs, or rather the number of dog deaths due to rabies, and  $N_D = S_D + I_D + R_D$  is the total number of dogs. Note that  $N = N_H + N_D$  which is the total number of both humans and dogs. Now  $\beta_{DH}$  is the infection rate between dogs and humans,  $\beta_D$  is the infection rate between dogs, since one dog can also infect another dog,  $\alpha_H$  is the recovery rate for humans, or rather the death rate,  $\alpha_D$  is the recovery rate for dogs, or rather the death rate,  $\Lambda_H$  is the birth rate for humans per year,  $\mu_H$  is the natural death rate for humans per year,  $\Lambda_D$  is the birth rate for dogs per year, and  $\mu_D$  is the natural death rate for dogs per year. We have only included the interaction between dogs and human and the interaction between dogs and dogs, since there is no evidence that a human has spread rabies to a dog, hence no infection rate between humans and dogs in this model. We have also neglected the natural death rate in both the infection differentials and the recovered differentials, since once one has rabies, they will not recover from the disease to die a natural death.

Figure 3.11 is the human infection curve for this hybrid SIR model for Yunnan province. This model is more complex, since we have to estimate the average infection rate of rabies from dogs to humans, the average infection rate of rabies between dogs, the number of dogs needed to model this trend, the average birth rate and average natural death rate for humans, the average birth rate and average natural death rate for dogs, and the average recovery rate for dogs and humans.



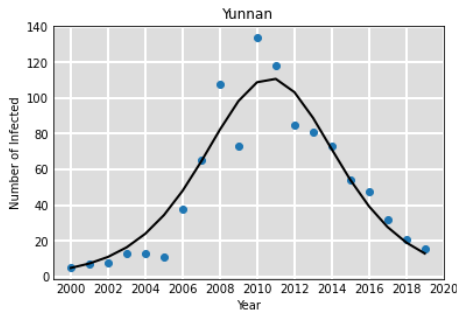


**Figure 3.11:** The Infection Curve for Yunnan using the Human-Dog Hybrid Model

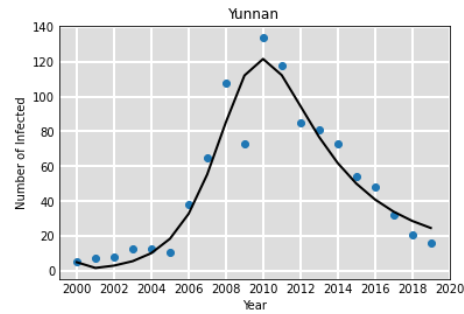
From Figure 3.11, we have the estimated infection rate for humans to be approximately 33 people are infected with rabies, by dogs, per year in Yunnan. The estimated death rate for humans due to rabies is also approximately 33 people per year in Yunnan. The estimated initial dog population is approximately 3,548,822 dogs in Yunnan, with approximately 456,872 of those dogs initially infected with rabies. Error estimation could not be easily calculated for these estimates due to the complexity of the model. Calculating these errors is a problem in which we are actively investigating for solutions. Comparing these results found in our model to the results found in a more comprehensive model investigating Yunnan, we see that our results are comparatively close [17]. In the comprehensive model, the estimated initial dog population was approximately 3,743,000, which is very close to the value that we found using equations (3.1) – (3.6). Our model is a relatively simple differential model, but we can achieve results close to the more complex discrete model established in the comprehensive model [17]. However, our results are very sensitive to initial conditions. If our initial parameter estimates are too far away, we will not get a good fit for our model due to estimating eleven different parameters with six differential equations.

Figure 3.12 is the infection curve for Yunnan using the simple SIR model found in section 3.1. Figure 3.13 is the infection curve for Yunnan using the human-dog hybrid model. As we can see, the more complex model appears to better capture the data.

This indicates that our human-dog hybrid model appears to better capture the general trend in the infection data, but without estimates on the error, we can not say with certainty. Let us now look to the high incidence provinces, using the human-

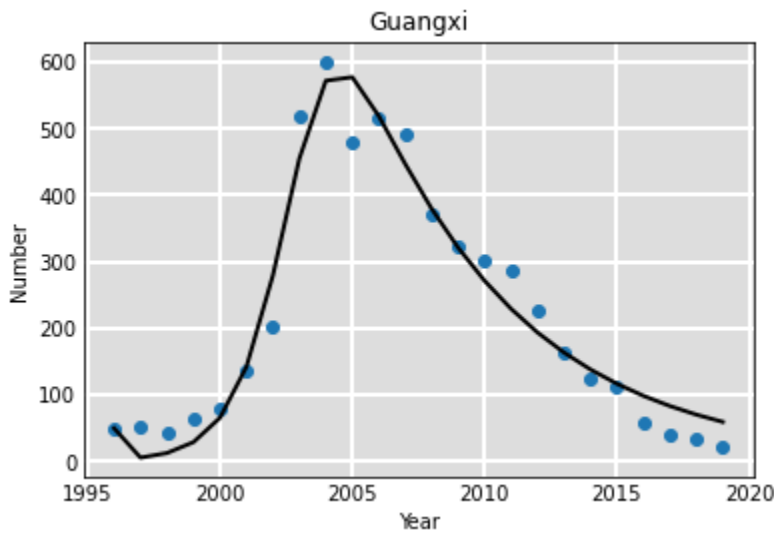


**Figure 3.12:** The Infection Curve for Yunnan (Simple SIR Model). Infection rate is 189 people per year.



**Figure 3.13:** The Infection Curve for Yunnan (Human-Dog Hybrid Model). Infection rate is 33 people per year.

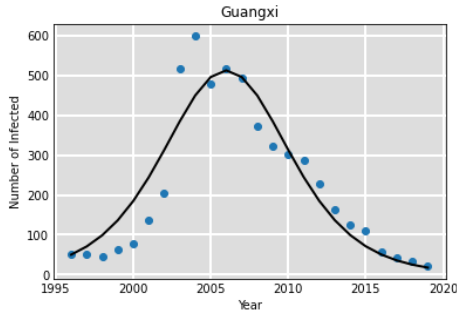
dog hybrid model. Figure 3.14 is the infection curve Guangxi.



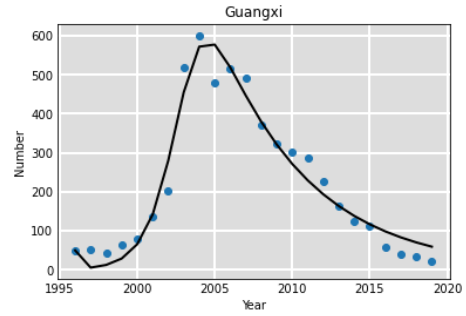
**Figure 3.14:** The Infection Curve for Guangxi using the Human-Dog Hybrid Model

The average rate of infection for rabies in Guangxi is approximately 20 people per year, with an average death rate of approximately 17 per year. The average number of people infected per year in Guangxi, using the simple SIR model, was found out to be about 79 people, with a corresponding average number of deaths to be around 79 people per year. Comparing the two models, Figures 3.15 and 3.16 are the infection curves for Guangxi using the simple SIR model and the human-dog hybrid model, respectively.

Comparing these infection curves, we see that the human-dog hybrid model appears to fit the data better, but we can not say with certainty due to being unable

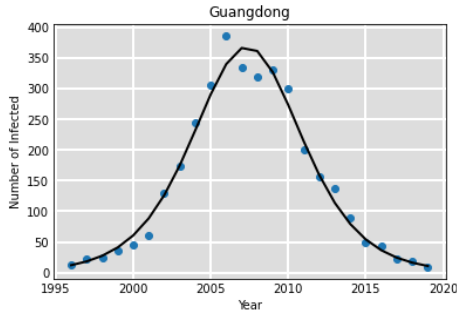


**Figure 3.15:** The Infection Curve for Guangxi (Simple SIR Model)

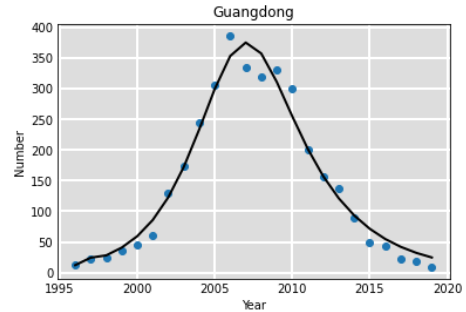


**Figure 3.16:** The Infection Curve for Guangxi (Human-Dog Hybrid Model)

to calculate uncertainties. The following figures are the comparisons between the simple SIR model and the human-dog hybrid model for the remaining high incidence provinces in China, along with the estimated infection and recovery rates.



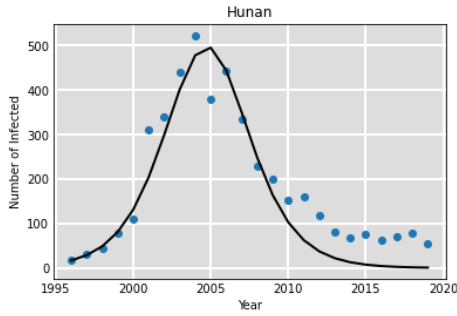
**Figure 3.17:** The Infection Curve for Guangdong (Simple SIR Model)



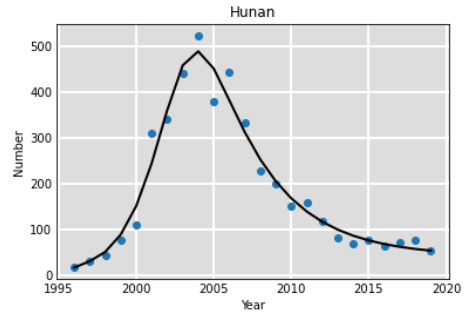
**Figure 3.18:** The Infection Curve for Guangdong (Human-Dog Hybrid Model)

From Figure 3.18, the average infection rate for Guangdong is approximately 25 people per year with an average recovery rate of 23 people per year. These values seem reasonable. From the simple SIR model for this province we found that the average infection rate to be approximately 151 people, with an average death rate of 151 people. Two different infection rates that both seem to fit the data relatively well.

From Figures 3.4 and 3.19, we found that the average number of people infected per year in Hunan, using the simple SIR model, was found to be about 140 people and the average number of deaths due to rabies per year to be about 140 people as well. From Figure 3.20, the average infection rate for Hunan is approximately 15 people per year with an average recovery rate of 26 people per year. The latter seems reasonable, but the discrepancy between the infection rate and recovery rate is not ideal. This leads to further investigation on whether there is under-reporting,

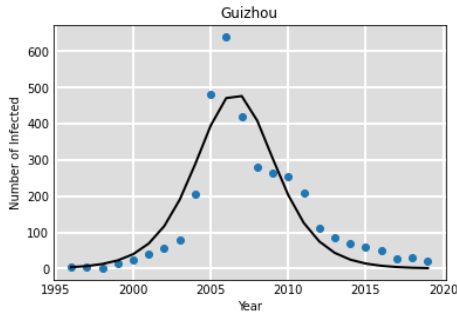


**Figure 3.19:** The Infection Curve for Hunan (Simple SIR Model)

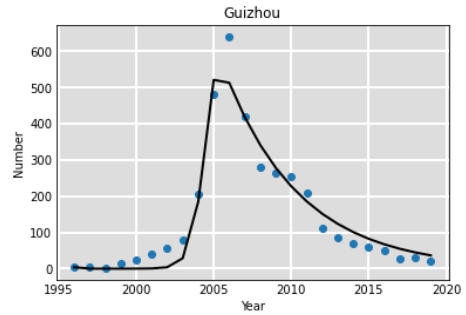


**Figure 3.20:** The Infection Curve for Hunan (Human-Dog Hybrid Model)

since the human-dog hybrid model indicates that there are more death due to rabies than infections due to rabies. This could also be due to some modeling assumptions that are incorrect.



**Figure 3.21:** The Infection Curve for Guizhou (Simple SIR Model)



**Figure 3.22:** The Infection Curve for Guizhou (Human-Dog Hybrid Model)

From Figures 3.3 and 3.21, we found that the average number of people infected per year in Guizhou is about 114 people and the average number of deaths due to rabies per year in Guizhou is about 114 people. From Figure 3.22, the average infection rate for Guizhou is approximately 12 people per year with an average recovery rate of 22 people per year. Same as Hunan, this leads to investigating whether there was under-reporting in Guizhou during this time, or if the model assumptions are incorrect.

## 4 DISCUSSION AND CONCLUSION

### 4.1 Conclusion

While we were successful in implementing a set of different models for investigating rabies data, we also did not achieve the original desired goal of this thesis. This was primarily a consequence of the surveillance data we were working with. As the results show, there are many issues when attempting to model complicated differential systems with limited data. Also, the simple SIR model gives us reasonable approximations for the average infection rate and average recovery rate for high incidence provinces, but does not take into account the fact that the way most humans become infected with rabies is through animal bites and scratches. The simple SIR model assumes that humans infect other humans with rabies, which is most likely not the case. The more complex dog-human hybrid SIR model gave some better fits for determining the infection rate in humans, however, the complexity leads to an over sensitivity in estimating parameters and calculating errors on our parameter estimates. The parameter estimates for the human-dog hybrid model in the high incidence provinces also indicate that more research is needed to determine whether there was under-reporting during this time, or if we need to reevaluate our model.

A further problem was the lack of detailed population data. For example, we were only able to access data at the provincial level. Additionally, there was a lack of available data on dogs, such as how many were vaccinated, an estimate on just how many wild or free roaming dogs there are in each province, or just a spatial distribution for the dogs. While finer resolution population data exists, together with the dog data, it was not readily obtainable, requiring access through an app that could only be downloaded on a phone with a Chinese SIM card. As our Chinese collaborators were focused on the ongoing Covid-19 pandemic and there was a lockdown on data sharing made this made it impossible to get access to additional surveillance databases in China.

This highlights the importance of open and well annotated data, together with the need for central repositories to allow integrated and searchable data. In this way, more accurate and informative surveillance models can be developed.

## 4.2 Future Work

We would like to get better dog estimates in each province, if possible, along with the distribution of the infections in each province, i.e. were the majority of infections in the middle of the province or along the borders of each province. More comprehensive information would lead to a much better model and understanding of when an outbreak would occur. On a similar note, looking at the possible under-reporting in some of the high incidence provinces. We would also like to look at an even more complex model to investigate the lineage replacement. One such model could be

$$\begin{aligned}
\frac{dS_H}{dt} &= \Lambda_H N_H - \mu_H S_H - \frac{\beta_{1DH} S_H I_{1D}}{N} - \frac{\beta_{2DH} S_H I_{2D}}{N} \\
\frac{dI_{1H}}{dt} &= \frac{\beta_{1DH} S_H I_{1D}}{N} - \alpha_{1H} I_{1H} \\
\frac{dI_{2H}}{dt} &= \frac{\beta_{2DH} S_H I_{2D}}{N} - \alpha_{2H} I_{2H} \\
\frac{dR_H}{dt} &= \alpha_{1H} I_{1H} + \alpha_{2H} I_{2H} \\
\frac{dS_D}{dt} &= \Lambda_D N_D - \mu_D S_D - \frac{\beta_{1D} S_D I_{1D}}{N_D} - \frac{\beta_{2D} S_D I_{2D}}{N_D} \\
\frac{dI_{1D}}{dt} &= \frac{\beta_{1D} S_D I_{1D}}{N_D} - \alpha_{1D} I_{1D} \\
\frac{dI_{2D}}{dt} &= \frac{\beta_{2D} S_D I_{2D}}{N_D} - \alpha_{2D} I_{2D} \\
\frac{dR_D}{dt} &= \alpha_{1D} I_{1D} + \alpha_{2D} I_{2D}
\end{aligned}$$

where  $S_H$  is the number of susceptible humans,  $I_{1H}$  is the number of humans infected with China I,  $I_{2H}$  is the number of humans infected with China II,  $R_H$  is the number recovered humans, or rather the number of human deaths due to rabies, and  $N_H = S_H + I_{1H} + I_{2H} + R_H$  is the total number of humans. Similarly,  $S_D$  is the number of susceptible dogs,  $I_{1D}$  is the number of dogs infected with China I,  $I_{2D}$  is the number of dogs infected with China II,  $R_D$  is the number of recovered dogs, or rather the number of dog deaths due to rabies, and  $N_D = S_D + I_{1D} + I_{2D} + R_D$  is the total number of dogs. Note that  $N = N_H + N_D$  which is the total number of both humans and dogs. Now  $\beta_{1DH}$  is the infection rate for China I from dogs to humans,  $\beta_{2DH}$  is the infection rate for China II from dogs to humans,  $\beta_{1D}$  is the infection rate for China I between dogs,  $\beta_{2D}$  is the infection rate for China II between dogs,  $\alpha_{1H}$  is the recovery rate for humans infected with China I, or rather the death rate,  $\alpha_{2H}$  is the recovery rate for humans infected

with China II,  $\alpha_{1D}$  is the recovery rate for dogs infected with China I, or rather the death rate,  $\alpha_{2D}$  is the recovery rate for dogs infected with China II,  $\Lambda_H$  is the birth rate for humans per year,  $\mu_H$  is the natural death rate for humans per year,  $\Lambda_D$  is the birth rate for dogs per year, and  $\mu_D$  is the natural death rate for dogs per year.

We should also look at reparameterizing the data. The populations in each province are much higher than the number of people infected with rabies. Reparameterizing could help with the large discrepancies found in infection rates for some provinces. We would also like to use Monte Carlo Simulation techniques for ease in calculating parameter estimates in this model and the human-dog hybrid model. We would ideally like to have more reliable error estimation in these complex models. Once these complex models for each province are implemented, we would then like to then look at a network model, considering that people and dogs did not just stay in their respective province throughout this time period. We would also like to investigate how the economic expansion that occurred between 1996 and 2010 in China affected the third epizootic wave. Did this economic boom lead to the increase in rabies in the more rural provinces? Did the increase in funds help to decrease the number of cases later in the wave? There are many questions that we would still like to answer, but these models and steps provided here are at least a start.

## **APPENDIX A**

Table 4.1 has the number of confirmed deaths due to rabies for the provinces in China as provided by the Chinese CDC. The years have been abbreviated for ease, i.e. 1996 is '96 and 2000 is '00. Table 4.2 is the population for each province on a scale of 100,000x. The years have been abbreviated similar to Table 4.1.



Table 4.1: Confirmed Rabies Cases 1996-2020

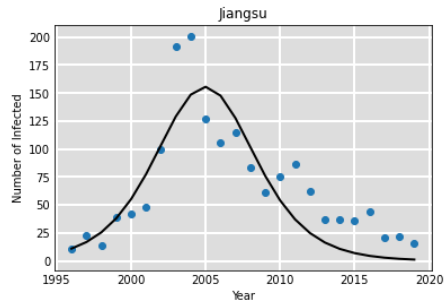
Province	'96	'97	'98	'99	'00	'01	'02	'03	'04	'05	'06	'07	'08	'09	'10	'11	'12	'13	'14	'15	'16	'17	'18	'19	'20
Guangxi	50	52	44	64	79	138	204	519	601	480	517	493	372	324	303	286	227	163	125	111	57	41	34	23	11
Hunan	17	32	43	78	111	311	341	441	523	379	443	334	229	200	152	160	119	82	68	76	64	71	78	55	59
Guizhou	4	6	0	15	25	41	57	80	206	481	641	419	281	263	254	210	113	85	71	61	51	26	31	21	10
Guangdong	12	22	25	36	45	60	130	173	245	306	387	334	319	330	301	201	157	138	90	49	44	23	18	8	6
Jiangxi	7	27	60	79	160	192	160	131	126	110	92	78	74	60	48	44	23	17	13	10	11	15	13	7	4
Hubei	1	16	14	4	4	19	20	104	224	184	218	151	90	120	84	87	56	39	39	37	32	39	34	22	11
Jiangsu	11	23	14	39	42	48	100	192	201	127	106	115	83	61	75	87	62	37	37	36	44	21	22	16	17
Henan	2	6	2	5	1	6	35	46	130	136	159	196	116	108	89	98	87	79	80	80	82	52	42	37	27
Sichuan	7	4	8	2	0	4	6	0	16	49	191	372	172	102	82	75	67	68	44	37	20	27	21	19	20
Anhui	1	3	1	4	5	4	53	206	182	94	115	83	39	55	48	50	38	31	32	33	23	39	17	23	11
Shandong	0	1	4	3	4	2	1	14	64	60	133	139	111	92	74	90	67	55	33	37	25	23	8	2	0
Hebei	9	3	2	0	1	2	5	2	7	12	86	144	110	135	121	94	66	67	57	42	31	8	11	4	1
Chongqing	0	0	0	0	0	0	0	0	2	6	28	175	173	125	94	85	48	31	29	27	21	24	18	13	0
Yunnan	0	1	0	1	5	7	8	13	13	11	38	65	108	73	134	118	85	81	73	54	48	32	21	16	6
Zhejiang	8	3	2	1	3	12	8	23	74	61	58	57	38	31	25	19	13	9	9	7	19	14	13	5	4
Hainan	3	2	1	0	1	1	2	12	7	4	7	64	106	46	70	45	28	29	21	8	4	5	0	1	0
Fujian	3	5	1	3	4	17	24	28	20	27	44	43	15	11	9	2	3	2	0	3	1	2	0	0	1
Shanxi	1	1	1	1	3	0	1	3	1	1	0	3	10	28	42	88	67	64	51	28	26	17	11	2	1
Shaanxi	0	4	1	2	6	2	1	1	1	3	1	0	0	26	21	41	46	50	30	26	14	17	18	13	7
Tianjin	0	0	0	0	0	0	1	0	0	3	4	18	10	11	4	8	9	4	5	2	5	2	0	0	1
Inner Mongolia	7	7	0	1	2	2	2	1	2	0	1	6	2	5	6	12	12	14	6	7	5	2	2	0	2
Shanghai	1	0	2	1	1	0	0	0	3	1	7	7	1	3	3	7	4	1	3	0	1	2	5	0	0
Beijing	0	0	0	0	0	0	0	0	0	1	1	3	6	3	9	5	13	7	7	10	3	2	3	1	1
Liaoning	1	1	1	2	2	0	1	0	2	0	0	0	0	0	0	2	6	4	2	3	0	0	0	0	0
Jilin	1	1	1	0	0	1	1	2	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Heilongjiang	2	1	0	1	0	0	0	0	0	0	2	0	0	0	0	0	1	1	0	0	0	0	0	1	0
Xinjiang	1	0	0	0	0	1	0	0	0	1	0	0	1	0	0	2	0	0	0	0	1	0	0	0	0
Gansu	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	9	4	11	8	9	1	0	1
Tibet	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0
Ningxia	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	2	3	8	14	7	2	1	1	1	1
Qinghai	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	1	0	0	0

Table 4.2: Population in China 1996-2019

Year	'96	'97	'98	'99	'00	'01	'02	'03	'04	'05	'06	'07	'08	'09	'10	'11	'12	'13	'14	'15	'16	'17	'18	'19
Beijing	126	124	125	126	138	138	142	146	149	154	158	163	170	176	196	202	207	212	215	217	217	217	215	215
Tianjin	95	95	96	96	100	100	101	101	102	104	106	112	118	123	130	136	141	147	152	155	156	156	156	156
Hebei	648	653	657	661	674	670	674	677	681	685	690	694	699	703	719	724	729	733	738	743	747	752	756	759
Shanxi	311	314	317	320	330	327	329	331	334	336	338	339	341	343	357	359	361	363	365	366	368	370	372	373
Neimenggu	231	233	235	236	238	238	238	238	238	239	240	240	241	242	247	248	249	250	251	251	252	253	253	254
Liaoning	412	414	416	417	424	419	420	421	422	422	427	430	432	432	438	438	439	439	439	438	438	437	436	435
Jilin	261	263	264	266	273	269	270	270	271	272	272	273	273	274	275	275	275	275	275	275	273	272	270	269
Heilongjiang	373	375	377	379	369	381	381	382	382	382	382	382	383	383	383	383	383	384	383	381	380	379	377	375
Shanghai	142	146	146	147	167	161	163	171	174	178	182	186	189	192	230	235	238	242	243	242	242	242	242	243
Jiangsu	711	715	718	721	744	736	738	741	743	748	755	763	768	773	787	790	792	794	796	798	800	803	805	807
Zhejiang	434	444	446	448	468	461	465	468	472	490	498	506	512	518	545	546	548	550	551	554	559	566	574	585
Anhui	607	613	618	624	599	633	634	641	646	612	611	612	614	613	596	597	599	603	608	614	620	626	632	637
Fujian	326	328	330	332	347	344	347	349	351	354	356	358	360	363	369	372	375	377	381	384	387	391	394	397
Jiangxi	411	415	419	423	414	419	422	425	428	431	434	437	440	443	446	449	450	452	454	457	459	462	465	467
Shandong	874	879	884	888	908	904	908	913	918	925	931	937	942	947	959	964	969	973	979	985	995	1000	1005	1007
Henan	917	924	932	939	926	956	961	967	972	938	939	936	943	949	941	939	941	941	944	948	953	956	961	964
Hubei	583	587	591	594	603	598	599	600	602	571	569	570	571	572	573	576	578	580	582	585	589	590	592	593
Hunan	643	647	650	653	644	660	663	666	670	633	634	636	638	641	657	660	664	669	674	678	682	686	690	692
Guangdong	696	705	714	727	864	778	786	795	830	919	930	945	954	964	1044	1051	1060	1064	1072	1085	1100	1117	1135	1152
Guangxi	459	463	468	471	449	479	482	486	489	466	472	477	482	486	461	465	468	472	475	480	484	489	493	496
Hainan	73	74	75	76	79	80	80	81	82	83	84	85	85	86	87	88	89	90	90	91	92	93	93	95
Chongqing	302	304	306	308	309	310	311	313	312	280	281	282	284	286	289	292	295	297	299	302	305	308	310	312
Sichuan	841	843	849	855	833	864	867	870	873	821	817	813	814	819	805	805	808	811	814	820	826	830	834	838
Guizhou	356	361	366	371	353	380	384	387	390	373	376	376	379	380	348	347	348	350	351	353	356	358	360	362
Yunnan	404	409	414	419	429	429	433	438	442	445	448	451	454	457	460	463	466	469	471	474	477	480	483	486
Xizang	24	25	25	26	26	26	27	27	27	28	28	28	29	29	30	30	31	31	32	32	33	34	34	35
Shaanxi	354	357	360	362	361	366	367	369	371	372	374	375	376	377	374	374	375	376	378	379	381	384	386	388
Gansu	247	249	252	254	256	258	259	260	262	259	261	262	263	264	256	256	258	258	259	260	261	263	264	265
Qinghai	49	50	50	51	52	52	53	53	54	54	55	55	55	56	56	57	57	59	58	59	59	60	60	61
Ningxia	52	53	54	54	56	56	57	58	59	60	60	61	62	63	63	64	65	65	66	67	68	68	69	70
Xinjiang	169	172	175	177	193	188	191	193	196	201	205	210	213	216	219	221	223	226	230	236	240	245	249	252

## APPENDIX B

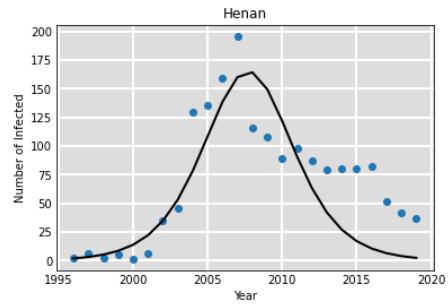
Below are the infection curves for the remaining moderate and some of the available mild incidence provinces in China with their estimated parameters using the Simple SIR Model. Note that in Figures 4.8 and 4.9, we have a different time window we are looking at. The Python codes that were used to generate this data can be found at [github.com/christurner1/RabiesStrain](https://github.com/christurner1/RabiesStrain) [19].



**Figure 4.1:** The Infection Curve for Jiangsu.

$$\beta = 221.09 \pm 9.00$$

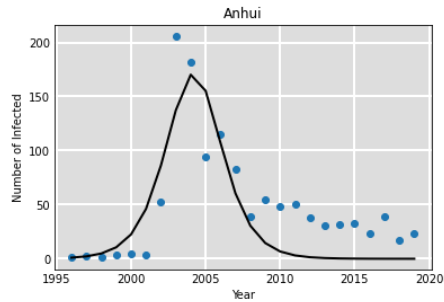
$$\alpha = 220.66 \pm 9.00$$



**Figure 4.2:** The Infection Curve for Henan.

$$\beta = 264.67 \pm 0.14$$

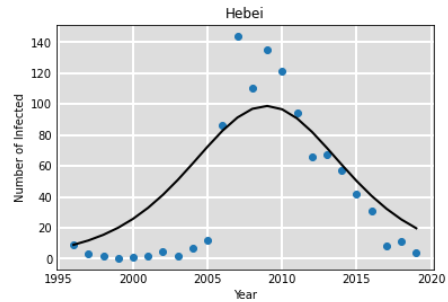
$$\alpha = 264.18 \pm 0.14$$



**Figure 4.3:** The Infection Curve for Anhui.

$$\beta = 337.75 \pm 0.14$$

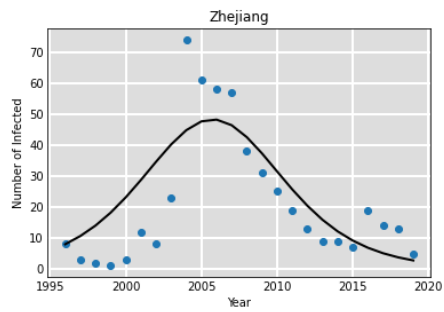
$$\alpha = 336.96 \pm .13$$



**Figure 4.4:** The Infection Curve for Hebei.

$$\beta = 171.95 \pm 8.40$$

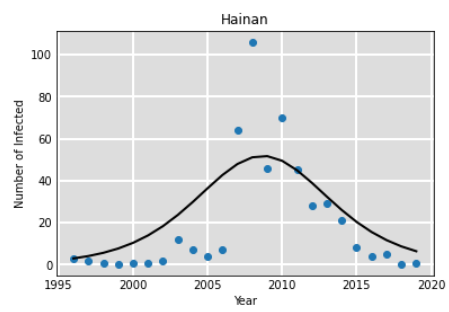
$$\alpha = 171.67 \pm 8.39$$



**Figure 4.5:** The Infection Curve for Zhejiang.

$$\beta = 230.84 \pm 10.72$$

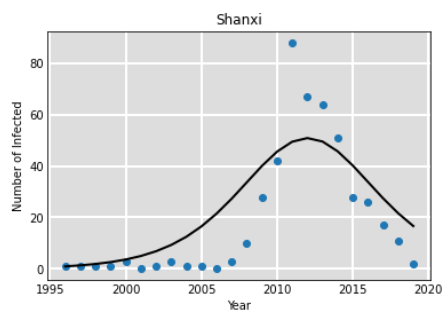
$$\alpha = 230.55 \pm 10.70$$



**Figure 4.6:** The Infection Curve for Hebei.

$$\beta = 94.75 \pm 6.36$$

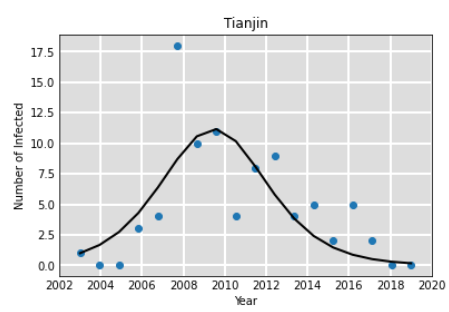
$$\alpha = 94.42 \pm 6.35$$



**Figure 4.7:** The Infection Curve for Shanxi.

$$\beta = 192.87 \pm 11.62$$

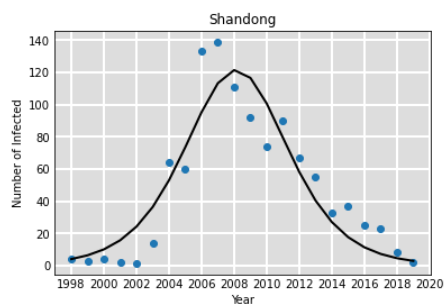
$$\alpha = 192.54 \pm 11.60$$



**Figure 4.8:** The Infection Curve for Tianjin.

$$\beta = 444.22 \pm .16$$

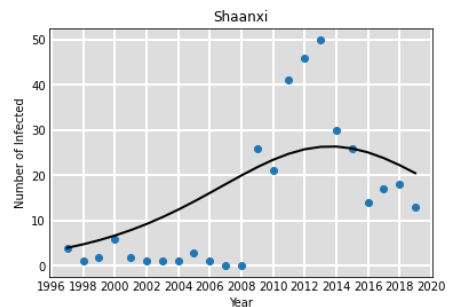
$$\alpha = 443.66 \pm .16$$



**Figure 4.9:** The Infection Curve for Shandong.

$$\beta = 294.86 \pm 9.17$$

$$\alpha = 294.39 \pm 9.16$$



**Figure 4.10:** The Infection Curve for Shaanxi.

$$\beta = 161.36 \pm 9.96$$

$$\alpha = 161.18 \pm 9.94$$

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## VITA

Christopher Turner began undergraduate courses at Angelo State University in San Angelo, Texas. He completed his Bachelor of Science in Mathematics in December 2016. Christopher entered full time into the Graduate School of Stephen F. Austin State University in Fall 2018 and received the degree of Master of Science in May 2020.

The style manual used in this thesis is A Manual For Authors of Mathematical Papers published by the American Mathematical Society.

This thesis was prepared by Christopher Turner using  $\text{\LaTeX}$ .