

Estimation of parameters related to SFTSV (severe febrile thrombocytopenia syndrome virus) transmission of sheep in Shandong, China

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Abstract: In this study, it has been carried out that estimation of mathematical models of SFTSV (severe febrile thrombocytopenia syndrome virus) transmission between sheep in Shandong, China. Data used in the system identification is obtained by observing the cohort group of sheep in Shandong Province, China by Chinese scientists. Observation of the cohort was carried out approximately every week, and it was measured that the number of SFTSV antibody positive animals. As a mathematical model, endemic SIR model was selected. System identification is performed using the solver function of the spreadsheet. The software and solver were Microsoft Excel2010 and GRG (Generalized Reduced Gradient) nonlinear method. After complemented of observed values with polynomial curve, logistic curve and the Gompertz curves, the system identification was conducted and initial values of parameters and initial value of variable were estimated. As the result of system identification, the value of basic reproduction indicating virus transmission was estimated as the value of 34-45. This system identification is included many estimation. However the result suggested that this disease has strong infectious force.

Keywords: SFTS, Severe Febrile Thrombocytopenia Syndrome, Sheep, Infectious Disease, Sir Model, Endemic Sir Model, Mathematical Model of Infectious Disease

1. Introduction

Severe fever with thrombocytopenia syndrome virus (SFTSV) is a newly identified pathogenic member of the Phlebovirus species in the family Bunyaviridae, which in humans causes fever with thrombocytopenia syndrome (SFTS) [1]. The common signs and symptoms of SFTS include high fever, gastrointestinal symptoms, thrombocytopenia, leukocytopenia, and multiorgan dysfunction with an average case-fatality rate of 10%–16%, according to the information system for disease control and prevention, Chinese Center for Disease Control and

Prevention (China CDC). In severe SFTS cases, neural symptoms, hemorrhages, disseminated intravascular coagulation, and multiorgan failure can occur and may result in death [2]. SFTS (Severe Fever with Thrombocytopenia Syndrome) is an infectious disease that is caused by the SFTSV (SFTS virus) classified in the family of Bunyaviridae Phlebovirus. This disease detected in central China in 2009, and the pathogen of this disease was identified by Yu et al. [1] in 2011.

The life cycle of the SFTSV is not yet known, but seems most likely to involve arthropod vectors and mammalian hosts, including wild and domesticated animal [3]. SFTSV

RNA has been detected in the ticks collected from domestic animals, including cattle, goats, and dogs [4, 5]. SFTSV was not detected in mosquitoes [4]. SFTSV has not been detected in tick eggs and has been detected in only tick collected from vegetation [5]. The arthropods positive for SFTSV suggest that they could be vectors of SFTSV or that they could acquire SFTSV from infected animals [6].

The survey of SFTSV antibody hold situation of wild and domestic animals by Cui *et al.* [6] shows the high positive percentage in goats (95%). And they suggested that goats might be important role in transmission of SFTSV.

To investigate the infections of severe fever with thrombocytopenia syndrome virus (SFTSV) in domesticated animals, Niu *et al.* [7] sampled a total of 3,039 animals in 2 counties in Shandong Province, People's Republic of China, from April to November 2011. In addition, to monitor new infections of SFTSV, a cohort of 38 sheep negative for SFTSV viral RNA and antibodies was established, and the animals were sampled every 10 days from June 20 through November 30.

The objectives of our study is to be analyzed these epidemiological studies conducted by Niu *et al.* [7] using a mathematical model of infectious disease.

2. Materials and Methods

2.1. The Data Used in Estimation of Parameters of SFTSV Transmission

The data of the time course of antibody-positive individuals SFTS virus to be able to put sheep cohort observed in 2011 in Shandong Province, China collected by Niu *et al.* [7] were used in this study. They observed changes in the antibody positive rate of SFTSV in cohort sheep group at 2 cities (Laizhou, $n = 17$; Penglai, $n = 21$), Shandong Province, China. Cohort sheep group were established with 38 sheep negative for SFTSV viral RNA and antibodies. According to the appendix of the report [7], the population of sheep in Laizhou and Penglai were 63,700 and 25,000 respectively.

Niu *et al.* [7] shows the changes of antibody-positive rate by graph in their report. We convert this graph to quantitative data using image processing.

2.2. The Model Used in Estimation of Parameters of SFTSV Transmission

In this study, endemic SIR model was used as a mathematical model. This model shows as a simultaneous differential equation (1.1-3). This model was obtained to insert the natural increase and decrease of population to the SIR model proposed by Kermack and McKendrick [8]. This model is applied to endemic that is limited to a narrow range locally, the number of patients is relatively small, and slowly speed relatively.

$$dS/dt = b - \mu S - \beta SI \quad (1.1)$$

$$dI/dt = \beta SI - (\gamma + \mu)I \quad (1.2)$$

$$dR/dt = -\mu R + \gamma I \quad (1.3)$$

In this model, S, I, R show the number of animals in susceptible, infected and recovered respectively. And β and γ show transmission rate of the virus and rate of recovery. b and μ show the natural increase and decrease of population.

The data used in this analysis, to distinguish the R and I It is difficult. Therefore, ignoring the change to R from I, β and the initial values of R and I were estimated.

Normally, vector-mediated model should be applied in this study. However, to apply vector-mediated model, information of vector arthropod is essential. In this analysis, expected transmission is as follows.

1. Infection through the vector arthropod (Arthropod vector is assumed to receive a virus from sheep)
2. Direct infection of sheep from sheep

The model used in this study has been simplified, and includes the possibility of infection various routes. This model does not include the possibility of direct transmission from the reservoir, such as wild animals, to sheep. Simplified model can be used for describing mathematical characteristics of infectious disease that were not clear of the route of infection.

2.3. Algorithm Used in Estimation of Parameters of SFTSV Transmission

Procedures and analysis software used for analysis will be described solver such as used below.

2.3.1. Procedure for Analysis

- 1) From the graph showing the change of SFTSV antibody positive rate of sheep cohort in the report [4], antibody retentions were quantified. In addition, it is multiplied by the sheep breeding population of both regions antibody positive rate, the negative rate, to determine the value of the entire region.
- 2) In order to increase the number of data used for system identification, data obtained by digitizing is interpolated. Polynomial curve, Growth curve of Gompertz and logistic curve were used in the interpolation.
- 3) The initial value of I and S indicates the infection rate β is estimated by using the Solver function in a spreadsheet.

The software used in the analysis is the Excel 2012 (Microsoft). The solver used in calculates is the GRG nonlinear model. The GRG nonlinear model is a technique that is generalized to non-linear programming problem, the reduction gradient method which has been handled in a linear programming problem.

2.4. The Parameters of Basically Population Dynamics of Animal

When using endemic SIR model and attempts to identify

the system, It is necessary to define the natural decline and increase of the population. In this section, it was described how to define the natural decline and natural increase of the population.

2.4.1. Birth Rate of Sheep

Birth rate b was assumed the product of the population of the region, ratio of female (0.5), number of lamb female gives birth to one year (1.0) and 1/365, according to the definition of the number of births per unit time.

2.4.2. Natural Mortality Rate of Sheep

In the case of livestock, the reduction due to natural mortality includes reduction by slaughter, due to other diseases and so on. In this report, we assumed that the total numbers of animal in these regions were maintained because of the difficult to access these data; number of slaughter or other disease.

2.5. Estimation of the Basic Reproduction Number (R0)

Basic reproduction number (R0) is defined as the average value of the secondary number of infections that develop with infection from an infected one person. It is utilized in public health as a value indicating clearly the appearance of the spread of infection. Estimation of the basic reproduction number was also carried out at the same time from the estimated values of the parameters obtained by the system identified in this study. Defining equations for the basic reproduction number varies depending on the mathematical model, in the case of endemic SIR model, R0 is defined by the following equation.

$$R_0 = \frac{\beta N}{\gamma + \mu} = \frac{\beta b}{\mu(\gamma + \mu)} \tag{2.1}$$

Table 1. Parameters in mathematical model of endemic SIR model.

Parameters	Definition
b	Number of births per unit time (day). =N×0.5×1× (1/365)
μ	The number of deaths does not depend on SFTS. =(b/N)
β	Transmission rate of the virus *
γ	Rate of recovery
S	Number of susceptible animals *
I	Number of infected animals *
R	Number of recovered animals =0
N	Total number of animals N=S+I+R

*The parameters estimated in this study.

3. Results

3.1. The parameters of SFTSV Transmission of Sheep to Sheep in Laizhou, Shandong, China

Estimate of the parameter and the initial value of the population of each category; I and S were shown in Table 2.

In the analysis of Laizhou City, indicating the value of the infection rate β was 5.62× 10-6 (polynomial), 5.24× 10-6 (logistic curve), 5.38× 10-6 (Gompertz curve) respectively. The interpolation method of each, the value of the basic reproduction R0, was 26.1, 24.4, 25.0.

In the analysis of Penglai City, indicating the value of the infection rate β was 2.45× 10-6 (polynomial curve), 2.46× 10-6 (logistic curve), 2.46× 10-6 (Gompertz curve) respectively. The interpolation method of each, the value of the basic reproduction R0, was 44.7, 44.9, 44.9.

3.2. Differences in Results of Analysis by Data Interpolation Method

Changes in SFTSV antibody-positive population in the sheep population cohort in Penglai City and Laizhou City and the curve drawn by the identified models were shown in Figure 1. Plotted each point were values actually observed, and curves were drawn on the basis of the parameters obtained by the system identification solid.

It was not significant difference in the results of analysis by data interpolation method together.

When the evaluation was performed on the data interpolation method by error sum of squares of the estimated value and the actual value of each data interpolation method, in the case of using a polynomial curve , the best results were obtained .

4. Discussion

4.1. Differences in Results of Analysis by Data Interpolation Method

Laizhou and Penglai city, a large difference in the analysis result data by the interpolation method were not observed, and the most small error sum of squares were obtained by polynomial curve as implemented methods. The order of the polynomial used in the present study is the third-order.

It is well known that the change in the number of infected individuals infection will be similar to growth curve as represented by Gompertz and logistic curve. Therefore, these growth curves were chose as the implemented methods.

However, when performing interpolation in Gompertz and logistic curve, it becomes complicated slightly matrix operations when compared to a polynomial curve. It was suggested the possibility of using a polynomial curve in reducing the computational load compere with Gompertz and logistic curve in case of building software to automatically cache simulation as the applications of this study.

Table 1. Estimated parameters of endemic SIR model in Laizhou and Penglai city, Shandong, China.

	Laizhou City				Penglai				Range
	polynomial	logistic	Gompertz	Median	polynomial	logistic	Gompertz	Median	
$S_0(10^3)$	58.2	60.3	59.0	59.0	20.4	20.7	20.5	20.5	—
$I_0(10^3)$	5.45	3.37	4.69	4.70	4.59	4.28	4.49	4.49	—
$\beta(10^{-6})$	5.62	5.24	5.38	5.40	2.45	2.46	2.46	2.46	2.45-5.6
R_0	26.1	24.4	25.0	25.0	44.7	44.9	44.9	44.9	24.4-44.

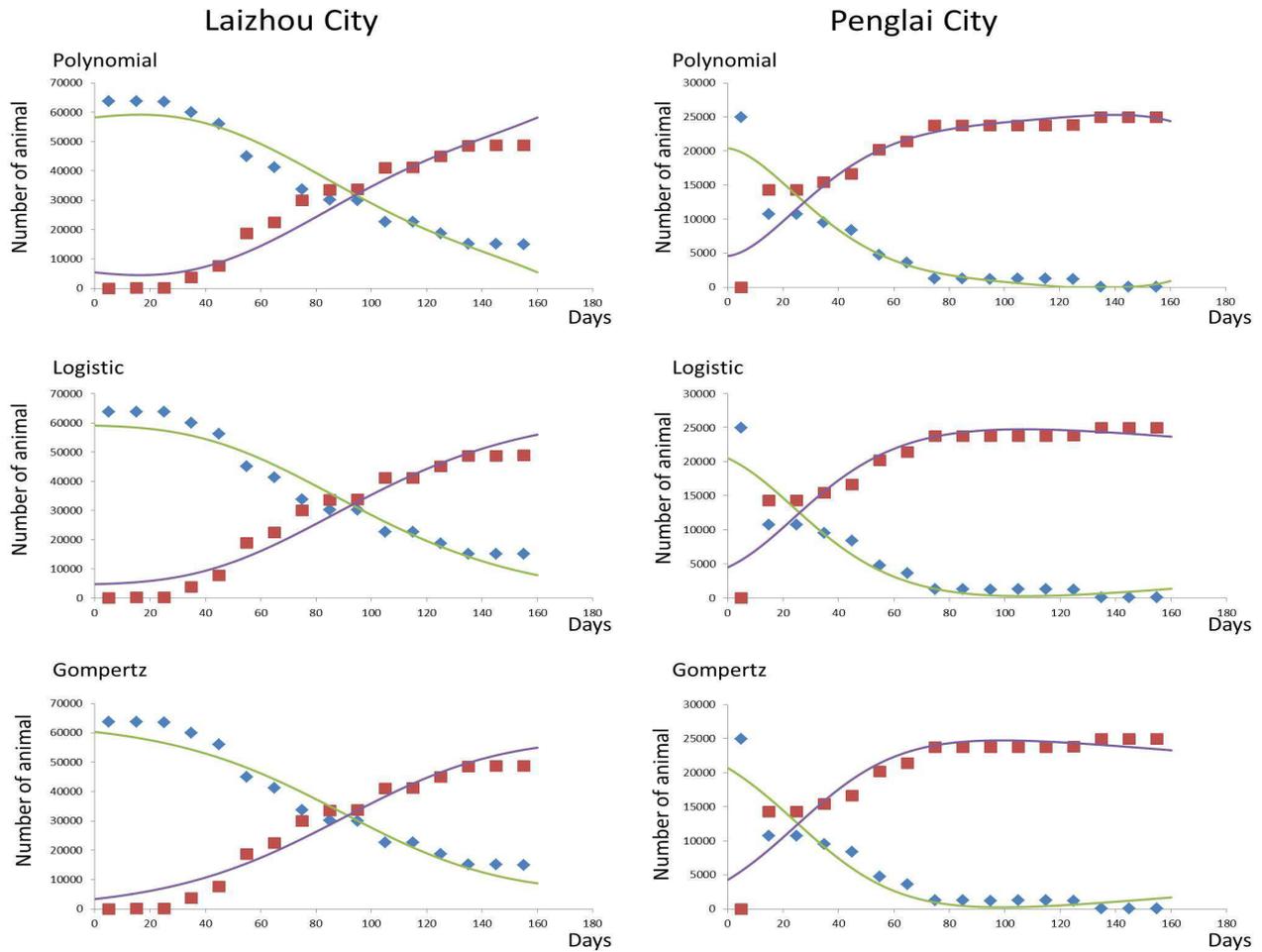


Fig 1. Changes in SFTSV antibody-positive number in the sheep cohort in Penglai and Laizhou City and predicted mathematical model. In this graph, ■ shows antibody-positive, ◆ shows antibody-negative, and liner shows the predicted mathematical models. The property of mathematical model were shown in Table 1.

4.2. Differences in Parameters in Penglai and Laizhou City

Large differences was observed with 25.0 and 44.9 in the basic reproduction number R_0 , 2.46 and 5.40 in the infection rate β , in this study. Because of the data used for this analysis that obtained from observation of small group, and it is expected environment of each of the two cities may be different, but it seems to expended relatively quickly in Penglai city. SFTS is an infection of insect mediated by ticks, is strongly affected by population density and activity of ticks in the spread of infection. Therefore, it can be considered that a difference in the basic reproduction number caused by insect vectors such as the

habitat of ticks. It is desired that research and analysis including data such as the habitat of ticks.

4.3. Estimation of Basic Reproduction Number R_0

We were able to obtain an estimate of 24.4-44.9 as the basic reproduction number of SFTS in this study. Basic reproduction number is defined as the average value of the secondary number of infections that develop with infection from an infected one person. Basic reproduction number of measles that has very strong infectivity and well-known as infectious diseases that need attention in public health has been estimated to be 12-18. In addition, a value of 38.4 has been reported in the foot-and-mouth disease infectivity is feared most strongly among the livestock infection. In

comparison with such values, spread of SFTSV which means can progress very rapidly. The survey SFTS in Japan suggested that potential wildlife like deer and wild boar plays an important role in the infection route rather than domestic animals. It is not possible to compare unconditionally because their density rearing environment also vary greatly in the wild animals and livestock. However, it may be necessary to discuss the need of quarantine system that considers the relatively high speed of infection on SFTSV animal to animal.

In addition, it seems to be big that the value of the basic reproduction number in our estimation, despite of the insect vector transmission type. A vector is an organism that does not cause disease itself but that transmits infection by conveying pathogens from one host to another. It would be understood to be smaller than the type of infection directly from animal to animal like a foot-and-mouth disease and measles that the rate of spread of vector borne transmission. Pathway mediated by insects has been the most promising as a route of infection of SFTS. However, it may be necessary to consider the route of infection contagious in animal, since the blood borne during processing bodies has been reported in human's case.

SFTS has unclear point such as the route of infection and presences of the reservoir in nature, our estimation contain some limitation. One of them is a prerequisite of infection route that includes to the sheep from sheep or through the arthropod vector. If livestock infected unilaterally from the reservoir that exist in nature, the meaning of our estimation would be decrease in meaning.

If new information of SFTS like a route of infection, it will be obtained newly mathematical model that matched the actual situation. And, such a model would be useful to assess the risk of SFTS, to determine the work of public health.

5. Conclusion

In this paper, we investigated the mathematical analysis of the spreading phenomenon of epidemiological studies of SFTS conducted by Niu et al[7]. We carried out the least square parameter estimation method to apply the endemic SIR model, observed in the time course of SFTSV antibody-positive populations in sheep cohort observed in Shandong Province, in China. As a result, we got an estimated numbers of 24.4-44.6 as the basic reproduction number that is a indicator of infection spreading rate of disease.

In the future, we will carry out practical research and risk analysis in various regions, and in parallel to perform the analysis of the relation between the occurrence of disease and economic loss.

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