Association between Hemorrhagic Fever with Renal Syndrome Epidemic and Climate Factors in Heilongjiang Province, China

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Abstract. The purpose of this study was to quantify the relationship between climate variation and transmission of hemorrhagic fever with renal syndrome (HFRS) in Heilongjiang Province, a highly endemic area for HFRS in China. Monthly notified HFRS cases and climatic data for 2001–2009 in Heilongjiang Province were collected. Using a seasonal autoregressive integrated moving average model, we found that relative humidity with a one-month lag ($\beta = -0.010$, $P = 0.003$) and a three-month lag ($\beta = 0.008$, $P = 0.003$), maximum temperature with a two-month lag ($\beta = 0.082$, $P = 0.028$), and southern oscillation index with a two-month lag ($\beta = -0.048$, $P = 0.019$) were significantly associated with HFRS transmission. Our study also showed that predicted values expected under the seasonal autoregressive integrated moving average model were highly consistent with observed values (Adjusted $R^2 = 83\%$, root mean squared error = 108). Thus, findings may help add to the knowledge gap of the role of climate factors in HFRS transmission in China and also assist national local health authorities in the development/refinement of a better strategy to prevent HFRS transmission.

INTRODUCTION

Hemorrhagic fever with renal syndrome (HFRS), is caused by different species of hantavirus transmitted by rodents, which can lead to severe clinical symptoms of fever, hemorrhage, and acute renal dysfunction.¹ This disease is found in more than 30 countries and has become a major public health problem in China.^{2,3} It is endemic to 28 of 31 provinces in China, accounts for 90% of the HFRS cases reported globally, and has a case-fatality rate of 3–10%.⁴ In China, HFRS is caused mainly by two types of hantaviruses, Hantaan virus and Seoul virus, which coevolved with distinct rodent hosts. Hantaan virus is associated with *Apodemus agrarius*, whereas Seoul virus is associated with *Rattus norvegicus* and often causes a less severe symptom.^{1,4} Although prevention and control measures such as rodent control, vaccination, and environmental management have been implemented in parts of China most at risk, HFRS remains as a serious public health problem and there are approximately 20,000–50,000 new cases annually.

The incidence of HFRS in China varies geographically, seasonally, and interannually and is influenced by density of the rodent population, prevalence of hantavirus infection in rodents, and contact rate between rodents and humans.^{5,6} Although the infection rate and population dynamics of rodents are believed to be influenced by climatic factors,^{7–13} the association between climate and host populations is complex in most places.¹⁴

Studies in different areas have suggested that climate factors, such as temperature, precipitation, and relative humidity, may influence the incidence of HFRS.^{6–8} However, the role of climate factors in the transmission of HFRS differs in different regions.^{4,6–12} For example, increased grass seed production followed by heavy precipitation, as a result of the El Niño

Southern Oscillation (ENSO), was found to be associated with higher *Peromyscus maniculatus* rodent density in southwestern United States and provides reservoirs for Sin Nombre virus.^{13,15–17} However, this result was not duplicated in other areas in the United States.¹⁴ In addition, a study in west-central Europe indicated that increased mean temperatures had a positive relationship with the outbreak of Puumala hantavirus infections through high seed production and high bank vole densities. However, other studies in Scandinavia have shown that warm winters led to a decrease in vole populations as a result of the decrease in protective snow cover.^{18,19} Moreover, studies in eastern China showed that excessive precipitation could have a negative impact on rodents by destroying their habitats.^{8,20} In addition, temperature, vegetation type, land use, and ENSO have been shown to be associated with the transmission of HFRS in China.^{4,6,7,21} Therefore, climate variables related to rodent population dynamics may serve as indicators for the risk of HFRS transmission in humans.^{22–24}

Heilongjiang Province, which is a cold area in northeastern China, was the first identified epidemic foci of HFRS in China.² In the past few years, the incidence of HFRS in Heilongjiang Province remains high. In 2009, the number of HFRS report cases reached 1,701, which accounted for 20% of all cases in China. Until now, there have been no studies conducted that quantified the relationship between climate variation and transmission of HFRS in Heilongjiang Province and few studies in China.^{7,8,20,21,25}

The purpose of this study was to quantify the relationship between incidence of HFRS and climate in Heilongjiang Province. An additional objective was to develop a climate-based epidemic forecasting model to assist monitoring of HFRS incidence in the region to inform public health policy in Heilongjiang Province on the basis of changes in particular environmental variables.

MATERIALS AND METHODS

Study areas. Heilongjiang Province (121°11'–135°5'E, 43°25'–53°33'N) includes 13 cities and 66 counties with a population of 38.13 million. It has an area of 4546 km², of which 51% is forest and 30% is farmland. The climate in Heilongjiang

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Province is a monsoon climate, with an average annual temperature between -4°C and 5°C . The annual temperature during the summer is $16\text{--}23^{\circ}\text{C}$, and rainfall during the summer accounts for 65% of all the total precipitation in a year. No significant difference in rainfall was found between southern and northern regions; this difference was greater between eastern and west regions. The annual average relative humidity is 60–70%, and there is a similar spatial distribution feature for relative humidity as for rainfall. In addition, there are 32 meteorologic stations in Heilongjiang Province.

Data collection. Monthly numbers of HFRS cases in the 13 cities and 66 counties in Heilongjiang Province during January 2001–December 2009 were collected by the Center for Disease Control and Prevention of Heilongjiang Province. In this study, all the HFRS cases were confirmed according to the diagnosis from the Ministry of Health of the People's Republic of China.¹ A confirmed case of HFRS was defined as illness in a person who had traveled to an HFRS-endemic area or who had come into contact with rodent feces, saliva, and urine within two months before onset of illness, and who had an acute illness characterized by abrupt onset of at least two of the following clinical features: fever, chills, hemorrhage, headache, back pain, abdominal pain, acute renal dysfunction, and hypotension. In addition, the person had to have had at least one of the laboratory criteria for diagnosis: a positive result for hantavirus-specific IgM, or a four-fold increase in titers of hantavirus-specific IgG, or a positive result for hantavirus-specific RNA acid by reverse transcription–polymerase chain reaction in clinical specimens, or hantavirus isolated from clinical specimens.¹ Demographic data were obtained from the Heilongjiang Provincial Bureau of Statistics.

Monthly climatic data from 2001 through 2009 in Heilongjiang Province, including monthly mean temperature ($^{\circ}\text{C}$), monthly maximum temperature ($^{\circ}\text{C}$), monthly minimum temperature ($^{\circ}\text{C}$), monthly relative humidity (%) and monthly rainfall (rainfall, mm), were obtained from the Chinese Bureau of Meteorology. Temperature was measured four times per day at 2:00 AM, 8:00 AM, noon, and 8:00 PM. Mean daily temperature is defined as the average of the four values. Mean monthly temperature is defined as the average of the mean daily temperature of every month. Maximum and minimum monthly and daily temperatures were also obtained. Monthly rainfall is defined as total precipitation every month, including rain and snow. Daily relative humidity is defined as average relative humidity at 2:00 AM, 8:00 AM, noon, and 8:00 PM, and monthly relative humidity is the average of the daily relative humidity of every month. In this study, we used the average of each climatic variable measured at the 32 meteorologic stations to explore the association between climate variables and incidence of HFRS by using the seasonal autoregressive integrated moving average (SARIMA) models. Southern oscillation index (SOI) was used as an indicator of ENSO, the most important coupled ocean–atmosphere phenomenon that affects the climate in China.²⁴ The SOI was provided by the Climate Prediction Center of the National Weather Service.²⁶

Statistical analysis. Time series analysis has been extensively used to study the association between climate variability and disease transmission.^{25,27,28} More specifically, the SARIMA models are an available approach for interpreting and applying surveillance data in disease control, prevention, and forecast.²⁹ The SARIMA models are especially useful in modeling the temporal-dependent structure of time series

data with the adjustment of the impact of seasonal and interannual tendency.³⁰

The SARIMA models have been successfully applied to predict the incidence of infectious diseases. A SARIMA model with nonseasonal and seasonal factors is denoted by $\text{ARIMA}(p, d, q) \times (P, D, Q)_s$, where the term (p, d, q) gives the order of nonseasonal part, $(P, D, Q)_s$ gives the order of seasonal part, and s is the number of observations in a seasonal cycle. The modeling of SARIMA involved identification, estimation, diagnostic checking, and forecasting stages, corresponding to the stages described by Box and Jenkins.²⁹ The autocorrelation function (ACF) and partial autocorrelation function (PACF) were calculated to assess the appropriate orders of autocorrelation and moving average terms. Significance tests for parameter estimates indicate whether some terms in the model may be unnecessary. Goodness-of-fit statistics, such as R^2 , Akaike's Information Criterion (AIC), Schwarz Bayesian Information Criterion, root mean square error, mean absolute percent error and adjusted R^2 , aid in comparing this model to others. Tests for white noise residuals indicate whether the residual series contains additional information that might be used by a more complex model.

In this study, the climatic variables, including mean monthly temperature, maximum monthly temperature, minimum monthly temperature, monthly relative humidity, monthly rainfall, SOI, and corresponding lags of 1–6 months, were the final pool of candidate predictor variables. The best subsets procedure was applied to select predictors from candidate variables in this study. The general idea behind the best subsets method is that we select the subset of predictors that are best at meeting well-defined objective criterion, such as having the smallest AIC.^{31,32} In our study, all possible combinations of lags of climatic variables from one to six months were included to build different models, and the model with the smallest AIC value was considered the final model. The maximum-likelihood method was used for parameter estimation. The AIC was applied to compare goodness-of-fit within models. Furthermore, tests for white noise residuals with Box-Ljung test indicate whether the residual series contains additional information that might be used in a more complex model.

The number of HFRS cases was divided into two parts: data for January 2001–December 2008 were used to build the SARIMA model, and data for January–December 2009 were used to validate the model. A natural log transformation of the dependent variable, the monthly cases of HFRS, was conducted to meet the requirements of stationary and normality for the SARIMA model. In addition, the cubic root transformation was also applied to the monthly maximum temperature and SOI.^{25,27} In this study, data analysis was performed by using SAS version 9.2 software.³³

RESULTS

Descriptive analysis. There were 30,439 HFRS cases during 2001–2009 and an annual average incidence of 8.87 cases/100,000 population. There was seasonality in the number of cases during the study period. One peak of HFRS cases in winter (October–December) was observed and accounted for 53.8% of cases. Another peak appeared in summer (May–July) and accounted for 19.8% of cases. During January 2001–December 2009, monthly mean temperature, monthly maximum temperature, monthly minimum temperature, monthly relative humidity,

FIGURE 1. Number of hemorrhagic fever with renal syndrome cases and climate variables in Heilongjiang Province, China, 2001–2009.

monthly rainfall, and monthly SOI ranged between -24.2°C and 22.5°C , -18.4°C and 27.9°C , -29.4°C and 17.9°C , 39% and 81.6%, 0.23 mm and 192.08 mm, and -4.1 and 2.7 respectively. The temporal variation of climatic factors and the number of cases during the study period is shown in Figure 1.

Correlation analysis. The bivariate correlation analysis between climatic variables and HFERS was conducted by using cross-correlation analysis adjusted for seasonality. There were significant lag effects between the climatic factors and the monthly cases of HFERS (Table 1). The cross-correlation coefficient reached the maximum at the three-month lag or four-month lag.

SARIMA model. The results showed that first-order autoregression ($\beta = 0.748$, $P = 0.0001$) and seasonal autoregression ($\beta = 0.887$, $P = 0.0001$, lag = 12), relative humidity at one-month and three-month lags, monthly maximum temperature (curt root transformation) at two-month lag, and SOI (curt root transformation) at the two-month lag were significantly associated with transmission of HFERS, and other climatic variables, including monthly minimum temperature, rainfall, and monthly mean temperature, were not significantly associated (Table 2).

An autocorrelation check of residual with Box-Ljung test also showed that the model was appropriate ($\chi^2 = 4.94$, $P =$

0.2930). The ACF and PACF also showed that there was no significant autocorrelation between residuals at different lags in the final ARIMA model (Figure 2). The final model can be expressed as

$$(\log \text{ cases})_t = 5.290 + \frac{1}{(1 - 0.748B)(1 - 0.884B^{12})} a_t - 0.010RH_{t-1} + 0.008RH_{t-3} + 0.082\text{curt}(\text{MaxT})_{t-2} - 0.048\text{curt}(\text{SOI})_{t-2}$$

The number of monthly observed cases and that of fitted HFERS cases from the model in Heilongjiang Province was compared, and they matched reasonably well (Figure 3). The validation for January 2009 through December 2009 also showed good fitness between the observed and predicted values (Adjusted $R^2 = 83\%$, root mean square error = 108).

DISCUSSION

This study demonstrated that the number of monthly notified HFERS cases was associated with climate variability occurring

TABLE 1
Cross-correlation coefficients between climate variables and number of HFERS in Heilongjiang Province, China*

Climate variable	Lag 0	Lag 1	Lag 2	Lag 3	Lag 4	Lag 5	Lag 6
Mean T ($^{\circ}\text{C}$)	$-0.36^{\dagger}$	-0.06	$0.20^{\dagger}$	$0.37^{\dagger}$	$0.43^{\dagger\ddagger}$	$0.41^{\dagger}$	$0.32^{\dagger}$
Maximum T ($^{\circ}\text{C}$)	$-0.37^{\dagger}$	-0.06	$0.21^{\dagger}$	$0.36^{\dagger}$	$0.42^{\dagger}$	$0.41^{\dagger}$	$0.32^{\dagger}$
Minimum T ($^{\circ}\text{C}$)	$-0.34^{\dagger}$	-0.06	$0.20^{\dagger}$	$0.38^{\dagger}$	$0.45^{\dagger}$	$0.42^{\dagger}$	$0.31^{\dagger}$
Relative humidity (%)	0.05	$-0.19^{\dagger}$	0.00	0.40 †	0.51 †	0.17	$-0.30^{\dagger}$
Mean rainfall (mm)	$-0.28^{\dagger}$	-0.26	-0.08	0.33 †	0.62 †	0.44 †	0.14
SOI	-0.04	-0.09	-0.08	$-0.22^{\dagger\ddagger}$	$-0.20^{\dagger}$	-0.19	$-0.20^{\dagger}$

*HFERS = hemorrhagic fever with renal syndrome; T = temperature; SOI = southern oscillation index.

$^{\dagger}P < 0.05$.

‡ Maximum cross-correlation coefficient in each row.

TABLE 2
SARIMA regression of number of HFRS in Heilongjiang Province, China*

Model	β	SE	<i>t</i>	<i>P</i>	95% CI
Constant	5.290	0.502	10.532	0.0001	4.306–6.274
Autoregression, lag 1	0.748	0.070	10.624	0.0001	0.611–0.885
Seasonal autoregression, lag 12	0.887	0.037	24.087	0.0001	0.814–0.960
Relative humidity (%), 1-month lag	–0.010	0.003	–3.266	0.002	–0.016 to –0.004
Relative humidity (%), 3-month lag	0.008	0.003	2.426	0.017	0.002–0.014
Curt root (MaxT), 2-month lag	0.082	0.028	2.917	0.004	0.027–0.137
Curt root (SOI), 2-month lag	–0.048	0.019	–2.602	0.011	–0.085 to –0.011

*SARIMA = seasonal autoregressive integrated moving average model; HFRS = hemorrhagic fever with renal syndrome; CI = confidence interval; MaxT = monthly maximum temperature; SOI: southern oscillation index.

in the previous months. More importantly, after controlling the seasonal and autoregressive effect, our results showed an important seasonal signal in monthly maximum temperature, relative humidity, and SOI with a lag of 1–3 months in the association with reported HFRS cases. Identifying lag effects of climate variables included in our model will help local public health authorities to characterize the HFRS cases as they occur so as to reasonably forecast and prevent transmission of HFRS during epidemic seasons.

There is now a broad consensus that temperature factors are important in HFRS epidemics, but their association may vary among and within different areas.^{6,7,11,12} Some studies found that temperature had a positive effect,^{6,11} and others found a negative effect on HFRS incidence.^{7,12,13} The present study showed that monthly maximum temperature was positively associated with the monthly number of HFRS cases in this province, and other temperature factors, such as monthly minimum temperature and monthly mean temperature, were not included in the final model. A possible underlying mechanism for this finding is that temperature may affect the population density and hantavirus infection rate of rodents.^{9,14,34} Some studies reported that environmental variables, including temperature, may affect population dynamics of the deer mouse.¹⁴ Lower temperature in the winter may reduce the growth of rodents and the reproduction of hantavirus, and higher temperature may enable reservoirs to survive more easily in winters.

Some studies showed that hantavirus infections in rodents were biased toward older animals.^{34,35} For example, higher hantavirus prevalence was detected in older, heavier, male deer mice in the United States.³⁴ In addition, other studies have shown that rodent populations had a higher proportion of adults in spring–summer months than during the months of autumn and winter.^{35,36} As for the present study, monitoring the fluctuations of monthly maximum temperature in the area could be used as an indicator to temporally target the surveillance for HFRS infections.

Although one study reported that relative humidity may contribute to the high incidence of HFRS in northeastern China,²⁵ another study reported that associations between HFRS epidemics and precipitation, as well as relative humidity, were not significant.³⁷ In our study we found that relative humidity three months before analysis had a positive effect on the incidence of monthly HFRS cases, which was consistent with our previous study in northeastern China. Interestingly, we identified a negative effect of a relative humidity one-month lag on the monthly HFRS incidence. It is noteworthy that this negative effect was not found in a previous study in northeastern China.²⁸

The model suggested that SOI with a two-month lag was negatively associated with the transmission of HFRS in Heilongjiang Province. The SOI, computed from fluctuations in the surface air pressure difference between Tahiti and Darwin, Australia,

FIGURE 2. **A**, Autocorrelation and **B**, partial autocorrelation of residuals of the seasonal autoregressive integrated moving average model (SARIMA) model, Heilongjiang Province, China, 2001–2009.

FIGURE 3. Forecasted and observed number of hemorrhagic fever with renal syndrome (HFRS) cases based on a seasonal autoregressive integrated moving average model of climatic variation in Heilongjiang Province, China, 2001–2009.

indicates development and intensity of El Niño or La Niña events in the Pacific Ocean. Sustained negative values of SOI indicate El Niño episodes, whereas sustained positive values of SOI are typical of a La Niña episode.²⁶ It had been shown that ENSO was associated with other vector-borne diseases and zoonoses, such as malaria,^{38,39} dengue fever,^{40,41} Ross River virus infection,^{42,43} cutaneous leishmaniasis, and plague.^{44,45} Similarly, our results indicate that in addition to relative humidity and maximum temperature, SOI is also associated with HFRS incidence in Heilongjiang Province. Thus, local climate (e.g., temperature and humidity) was more likely to directly affect life cycle dynamics (e.g., reproductive rates and incubation periods) of the disease agents themselves, whereas larger-scale factors (e.g., SOI) could also influence broader ecologic processes and have possibly nonlinear impacts on disease transmission dynamics.^{18,46,47}

A clear association between rainfall and HFRS was not detected in this study. The association between HFRS epidemics and rainfall is still a matter of debate. Some studies showed that heavy rainfall followed by increased grass seed production was associated with higher deer mouse (*Peromyscus maniculatus*) densities, which caused an outbreak of hantavirus pulmonary syndrome in the Four Corners region of the United States,^{13,16,17} and a negative relationship between rainfall and HFRS has also been reported.⁸ There is no clear explanation for such difference, which may reflect heterogeneity in local climate conditions. Further studies should be conducted in different regions to gain a better understanding of the effect of rainfall on HFRS transmission.

We developed a SARIMA model of HFRS incidence, which could not only quantify the relationship between the climatic variables and HFRS, but also forecast the number of HFRS cases in Heilongjiang Province. The results showed that the SARIMA model was suitable in representing variation in HFRS

incidence in Heilongjiang Province during the study period because there was a good correlation between observed and predicted number of HFRS cases.

The results should be interpreted in light of the limitations of this study. First, although climate variables included in our model explain most variation in HFRS incidence in the region (as demonstrated by an adjusted R^2 of 83%), more detailed independent variables could have been used. For example, human activities, farming patterns, and rodent host density also affected the transmission of HFRS.^{2,16} However, because of the method of data collection and retrospective nature of the study, the aforementioned factors were not available. Second, the time-series data in our study were obtained from a passive surveillance system, and some HFRS patients with milder symptoms may have been missed. Third, the study focused on Heilongjiang Province in China. This particular model in our study may not apply to the other regions in China because local climate and habitat types are different; a separate analysis may be needed for each region of concern.

In our study, we formulated and tested a climate-based HFRS epidemic forecasting SARIMA model, which uses correlations and time lags between climate factors and HFRS incidence in Heilongjiang Province. Its predictive ability has important public health implications in that it will enable local public health officials to forecast HFRS reliably and enhance HFRS prevention strategies. Although this particular model may not apply to the other regions of concern because of local variability in climate and habitat, findings of the present study will provide directions for quantitatively predicting models for supplementing early warning system in other areas, where HFRS epidemic is vulnerable to the impact of climate change. Consequently, an accurate warning system would improve public health measures in developing countries.

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