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Temporal modeling of Crimean-Congo hemorrhagic fever in eastern Iran

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SUMMARY

Objectives: This study was conducted to determine the predicting factors of Crimean Congo hemorrhagic fever (CCHF) in Zabol and Zahedan, from where more than 60% of all national cases are reported, in order to improve CCHF disease surveillance and to target control efforts.
Methods: Data were collected from the National Reference Laboratory on Arboviruses and Viral Hemorrhagic Fevers, the national meteorology organization, the veterinary organization, and the national statistics center of Iran. A Poisson regression analysis was applied for the temporal modeling of human samples between 2000 and 2006. The modeling fitness was checked with data from 2007.
Results: This modeling revealed that the disease occurrence followed a seasonal pattern. The maximum temperature and relative humidity in previous months was found to positively affect the occurrence of the disease. Variables such as the level of livestock imports and the number of slaughtered animals were also found to be influential in the occurrence of the disease. The pseudo R^2 was 0.51 in the final model.
Conclusions: The model predicted the number of cases 1 month in advance with more or less acceptable accuracy. Therefore, it appears that the model might be useful as part of an early warning system.

1. Introduction

Crimean Congo Hemorrhagic Fever (CCHF) is a disease caused by a virus of the *Nairovirus* genus from the *Bunyaviridae* family. The virus commonly causes infection in domestic and wild livestock with no specific accompanying clinical symptoms. Thirty-one varieties of ticks, especially those of the genus *Hyalomma*, are the main vectors in nature. Human infection is acquired via a tick bite or following contact with an infected vertebrate, its blood, or other secretions. The fatality rate of the disease is reported to be about 30%.[1,2]

The first detection of antibodies to CCHF virus was reported in Iran in 1970.[3] Multiple serologic studies were subsequently conducted in Iran, which documented the presence of antibodies against the CCHF virus. However, due to the lack of sufficient attention and lack of a suitably equipped research center, this disease has been ignored since 1978 when it was first isolated from a tick in Ferdows, Khorasan Province.[4] The first instance of the clinical disease in Iran was documented in 1999, and since then, it has also been reported from other parts of the country.[5]

Of the 31 different tick species that are regarded as vectors for CCHF, most are found in Iran. The activity of *Hyalomma anatolicum anatolicum*, the most common Hyalomma in Iran, starts from early spring and reaches maximum activity in June and July, when it then starts to decrease again.[6] Contact with blood or infected viremic tissues of livestock (which have already acquired the disease from the ticks) and tick bites are the most common routes of human infection in Iran.[5]

Several studies have shown that the distribution of most infectious diseases (especially those that are transmitted via vectors) depends on climatic and environmental conditions and variations. To demonstrate such relationships and also to model them, comprehensive information on the reported cases of a particular disease and climatic variations of that region over a period of time is required. A climatic alteration that facilitates a vector's reproduction and consequently increases the incidence of the diseases transmitted via that particular vector is known as a factor.[7,8] Considering the rapid climatic changes in the earth's atmosphere, the influence of climatic factors on disease occurrence should be given more attention.[7] As climate change increases over the next half century and the related health research expands in scope, there will be useful evidence to direct policy.[9] Scientists have demonstrated that global warming is a risk factor for the distribution of vector-borne diseases to other

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regions and in increasing the number of cases in endemic areas.[1,7]

The transmission of infection for zoonotic diseases occurs when there is an overlap of activities between the reservoir, vector, and humans, and differs according to the pathogens and the location. Climate change may impact all of these stages and their interactions.[10] Climatic changes may have less influence on pathogen distribution than on animal or plant species distribution. This is due to the dependence of pathogens on other species, which is more important for vector-borne pathogens.[11]

CCHF epidemics are considered to be related to environmental and climatic changes that facilitate the survival of a large number of Hyalomma ticks and their immature and mature reservoirs.[12,13]

With an increasing demand for the design of early warning systems for diseases and recent improvements in the quality and quantity of meteorological and environmental data, the application of these systems has been considered by global health centers, and surveillance systems have been developed based upon them. An early diagnosis of an infectious disease is a key stage in conducting necessary interventions in order to decrease further infections and mortality in humans.[12,14]

Appropriate models can be effective in selecting the most efficient techniques for controlling a disease and understanding the life cycle of the causative infectious agent. An improvement in modeling may explain numerous superficial relationships via scientific methods, and in this regard, temporal modeling is one of the most common forms of modeling applied for diseases.[15] One of the most frequent temporal modeling methods used in epidemiology is time-series analysis. A time series is a collection of observations that have been ordered according to a specific time and at equal intervals. The most significant aim of time-series analysis is to predict values in the future. Regression analysis is a method of time series applied to show the relationship between two or more variables and also to make predictions. In addition to presenting the role of different variables, this type of analysis helps to predict the time of an epidemic in most infectious diseases, especially those transmitted via vectors.[16,17]

Although many studies have discussed the effects of environmental and climatic variables on diseases transmitted via vectors, and their distribution patterns, none have presented a temporal modeling of CCHF worldwide. Considering that more than 60% of all reported CCHF cases in Iran have derived from the cities of Zabol and Zahedan, and these two cities are regarded as the main focal point of the disease in this country, our study aimed to carry out temporal modeling using various available climatic and environmental data and applying time-series analysis.

2. Materials and methods

2.1. Study area

Sistan and Baluchestan Province is located in eastern Iran. Its long and hot summers, together with its short winters make it one of the driest provinces in Iran. Zahedan and Zabol, the northernmost cities of this province, are also the most crowded. The legal and illegal import of livestock takes place from eastern neighboring countries (Afghanistan and Pakistan) to these two cities.

2.2. Methods

In the present study, a CCHF case was defined as one confirmed with a positive IgM serologic test and/or positive by RT-PCR detection of viral RNA in the serum sample sent to the Laboratory of Arboviruses and Viral Hemorrhagic Fevers (National Reference Laboratory), Pasteur Institute of Iran, Tehran, Iran. Data from files relating to confirmed CCHF patients living in Zabol and Zahedan, who were referred to the laboratory between 2000 and 2007, were used.

To design the temporal model, Poisson regression was applied using Stata version 9.1. A Poisson regression analysis was applied to evaluate the effect of various environmental and climatic variables on disease occurrence, and the monthly number of infections was regarded as a dependent variable. To design the model, a stepwise method was used and the effect was calculated according to McFadden's pseudo R^2 and log likelihood. Variables with a p-value of less than 0.1 were entered into the model and variables with a p-value of less than 0.05 were considered significant and remained in the model. Excel (version 2007) was used to design the graphs.

The temperature data (monthly mean of maximum and minimum daily temperatures and the mean daily temperature in centigrade), the monthly mean amount of rain or snowfall (in cubic mm), and the mean amount of monthly relative humidity (percentage) were collected from the meteorological organization. The effect of these aforementioned variables on the occurrence of CCHF was assessed in a linear and non-linear way. The non-linear effect was calculated taking the squared value. The number of reported cases and the meteorological data during the past 1 to 6 months were registered into the model as predicting variables.

As the occurrence of CCHF in Zabol and Zahedan appeared to be affected by the import of livestock from neighboring countries (Pakistan and Afghanistan), an ordinal variable entitled 'import degree' was defined in our modeling; years with the highest amount of legal and illegal livestock import were ranked as 3; the years when legal import was banned and there was only a small amount of illegal import, due to strict supervision and restriction, were ranked as 1; other years with a status between 1 and 3 were ranked as 2. The data necessary for this ranking were collected via interviews with the authorities of the veterinary organization in Sistan and Baluchestan Province and also via searching the documents related to quarantine during these 9 years.

To discover the temporal trend of CCHF occurrence in confirmed cases, annual linear and non-linear effects were studied. To eliminate the collinearity between year and number of cases in each month, centralization was applied and 1999 was subtracted from all reported years of the disease. To assess the non-linear effect of the year, the second degree of this variable was used.

Seasonality was modeled using a sinusoidal transformation of time, including both $\sin(2\pi i/12)$ and $\cos(2\pi i/12)$ in the regression models, where 'i' was the month number (January = 1, and so on). This corresponds to a pattern with a period of 1 year, whose peak size and delay phase can be estimated from the regression coefficients.

Considering the fact that the two cities of Zabol and Zahedan have their own independent industrial slaughterhouses, the monthly data related to livestock slaughter in these two cities were collected from the veterinary organization in Sistan and Baluchestan Province and were used in the modeling.

The city code was also registered in the model as an independent variable.

In the designed model, the numbers of confirmed CCHF cases in each month were entered as dependent variables and the aforementioned variables during the 7 years (from 2000 to 2006) were registered as independent variables. The model validity was checked against the data from 2007. After designing the model, its goodness of fit was assessed by evaluating the residual graphs and comparing predicted and actual data.

3. Results

Between 2000 and 2007, 433 patients with CCHF were reported in Iran; of these, 60.7% (263 cases) were residents of Zabol and

Table 1
Pseudo R^2 values of Poisson regression for different models based on explanatory variables of CCHF cases in Zabol and Zahedan from 2000 to 2006; model 8 is the final model

Pseudo-R^2	Explanatory variables	Model number
0.15	Seasonal variation[a]	1
0.172	Model 1 + year[b] + squared value of year[b]	2
0.202	Model 2 + number of slaughtered animals/1000	3
0.292	Model 3 + import degree	4
0.343	Model 4 + maximum temperature with 1 month lag	5
0.361	Model 5 + relative humidity with 1 month lag	6
0.472	Model 6 + relative humidity with 6 months lag and its squared value	7
0.51	Model 7 + city code	8

CCHF, Crimean-Congo hemorrhagic fever.
[a] Sine and cosine conversions of the month.
[b] Year of the disease report minus 1999.

Zahedan: 33.9% Zabol (147 cases) and 26.8% Zahedan (116 cases). Seventeen percent (46 cases) of all reported cases were Afghan. The mean (± standard error) of annual reported cases in Zabol and Zahedan was 33.5 ± 8. The highest number of confirmed cases pertained to the years 2002 and 2007, whereas the lowest number was reported in the years 2000 (the first reported cases in the region) and 2004. During this period, there were 20 (7.5%) deaths in Zabol and Zahedan as a result of this disease.

To carry out the modeling, the dependent variable was firstly demonstrated to have a Poisson distribution and its variance and its mean almost equal ($p = 0.42$). Consequently, this type of regression was absolutely adequate for this sort of data.

Having eliminated those variables whose effect was not statistically significant, 10 explanatory variables remained in the model. Table 1 demonstrates the effect of adding each of the variables on pseudo R^2.

The model also illustrates that the sine and cosine conversions of the month, which represented the seasonal variations of the disease, would predict the temporal changes of the disease; in other words, seasonality was incorporated into the model by use of sine and cosine functions and this improved the model fit (Figure 1). It was revealed that this model has a lag period of 99 days; i.e., an increase in infections starts from April.

Adding the linear and non-linear (squared value) effect of the year and the number of slaughtered livestock (with the unit of 1000 animals) to each month increased the accuracy of the model (Table 1).

Furthermore, the model showed that when livestock import was more frequent from Afghanistan and Pakistan, the infection was more commonly observed in the two aforementioned cities, and the reverse when less frequent (pseudo $R^2 = 0.292$).

Adding the effect of climatic factors had the effect of increasing the pseudo R^2 of the model from 0.29 to 0.47. The maximum temperature of the previous month and the relative humidity of the previous month, as well as the previous 6 months, showed a positive correlation with cases of the disease.

The city code was influential in the number of monthly reported cases of the disease. As Zabol was given code 1 and Zahedan was given code 0, and the model's coefficient was positive, it was expected that, just as previously, cases of the disease would be more frequent in Zabol compared to Zahedan. The pseudo R^2 was 0.51 in the final model.

When the model was fitted to the data of 2007, this model was able to predict infections in that year in an appropriate way (Figure 2); the peaks and dips of the prediction and infection curves are in the same direction. The difference between the number of predicted and observed infections is shown in Figure 3. This figure

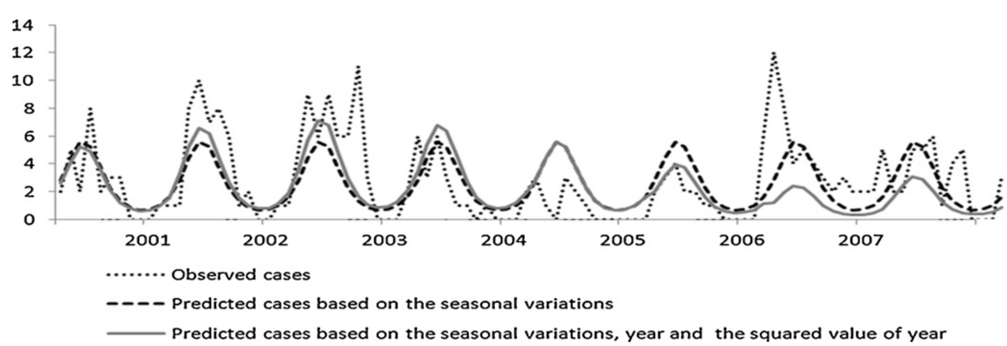

Figure 1. Observed reported cases of CCHF and predicted values from two different models of the disease.

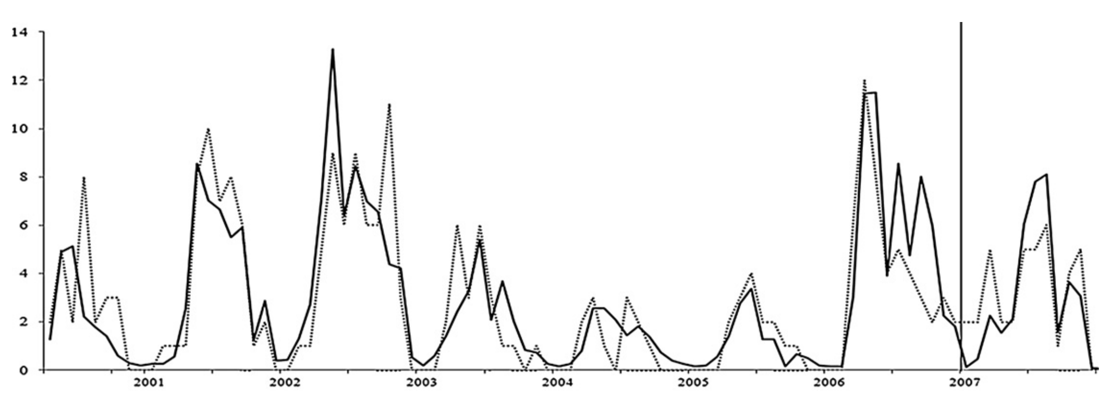

Figure 2. Observed reported cases of CCHF and predicted values based on the final model. The model was made based on data for 2000–2006 and its validity was checked with the data of year 2007.

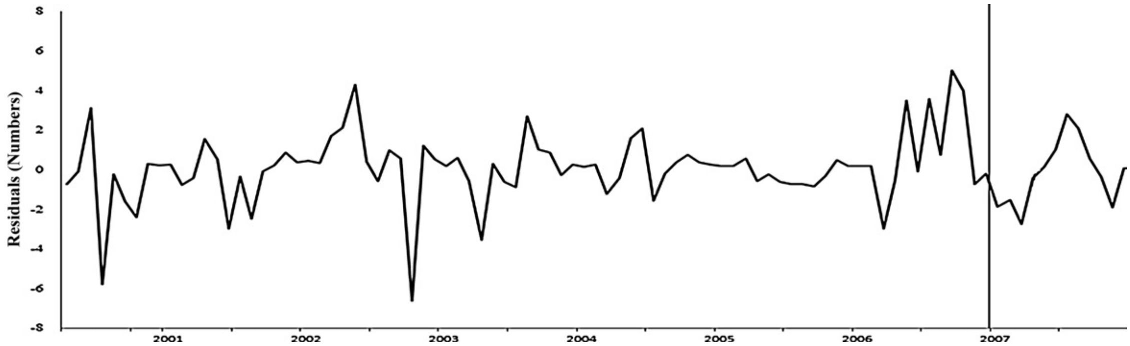

Figure 3. The discrepancy between observed and predicted values (residuals) for the final CCHF model (residuals were calculated as predicted minus observed cases). Negative values are indicative of underestimation. The model was made based on data for 2000–2006 and its validity was checked with the data of year 2007.

does not show obvious systematic changes over time, except for one period of poor performance in late 2002. We return to this period in the discussion. The mean amount of the subtraction of the number of observed cases from the number of predicted cases during these years (regardless of mathematical sign) was 1.32.

4. Discussion

The temporal modeling of CCHF in Zabol and Zahedan revealed that the occurrence of the disease followed seasonal variations, and like other diseases transmitted via vectors, was influenced by climatic factors. Variables such as levels of imports and the number of slaughtered livestock are regarded as explanatory variables in the occurrence of the disease. The results of this modeling could lead to improvements in the quality of control programs and surveillance of this disease.

The model also demonstrates that the sine and cosine conversions of the month, which represent seasonal variations of this disease, can predict temporal changes of the disease. Due to the fact that it is transmitted via ticks, and that variations result from the frequency and activity of ticks which are dependent on climatic changes in different seasons, such a seasonal pattern for this disease is anticipated and the results correspond to those of other similar studies.[18] In 2000, Haghdoost et al. conducted a time-series analysis which revealed that seasonal variations of malaria, which is also transmitted by insects, are an essential factor in the prediction of the status of the disease.[19] In another study in 2007, seasonal variations of tick infection rates were observed for human tick-borne pathogens relevant in Central Europe. This variation reflects the behavioral adaptation strategy of ticks.[20]

In the designed model, adding the linear and non-linear (squared) value of the year increased the model's accuracy; in other words, the secular trend of the disease had an ascending, followed by a descending, then again ascending trend bypass of time. Such a finding in a superficial evaluation of the trend of the confirmed and predicted cases is illustrated in Figure 1. There is a gap of 5 years between 2002 and 2007 – years with the peak number of predicted cases. The incidence of the disease follows a repeating pattern in some other parts of the world. For instance, since 1954 when the disease was reported for the first time in Kosovo, epidemics have repeated every 6 years.[21] To better clarify the long-term trend of the disease in Iran, sufficient time and evaluation of newly reported cases is essential.

The model presented the monthly number of slaughtered livestock as a predictor for the cases of that month. As the slaughtered animals in Zabol and Zahedan either belonged to those regions or were imported from neighboring countries, one would anticipate that with an increase in slaughter of potentially infected animals, the number of human cases would also rise. Considering that livestock import into the country is mainly for slaughter, such an index can be indirectly taken as an estimate of the amount of imported livestock. Taking this as a risk factor and also considering that the viremia period in livestock is 1 week and that the incubation period following tick bite is commonly 3–7 days, it is highly recommended to spray insecticide on the animal's body surface 2 weeks before slaughter and to avoid the slaughtering of febrile animals as they might be going through the viremia stage.

The addition of climatic factors also led to an increase in the model's accuracy. Atmosphere mostly affects the disease due to its influence on reservoir ticks. It is also possible that the contact pattern between humans, livestock, and ticks changes according to variations in temperature and humidity, which would consequently affect reported cases of the disease.[22] In this study, the maximum temperature of the previous month showed a positive correlation with cases of the disease. The growth cycle of the ticks is accelerated in warmer weather, whereas it is delayed in cool weather.[23] Considering that most reported cases of the disease occurred late in spring and early in summer, when there was a significant increase in temperature, a positive relationship between temperature and reported cases of the disease was anticipated. In addition, the model demonstrated that relative humidity during the previous month, as well as the previous 6 months, would positively affect the number of reported cases of the disease. Relative humidity influenced the tick's life cycle, either with respect to ovulation or hatching; even Hyalomma ticks select their particular hosts according to temperature and relative humidity and feed from them. Considering that Hyalomma is a resistant type of tick, very low or very high humidity is not ideal for its growth.[24,25] With respect to the dry climate of the area under study (with a relative humidity ranging from 20% to 50% in different months of the year), it was anticipated that tick reproduction would be higher during more humid months. However, to achieve further understanding of this issue and its relation to the maximum temperature of the previous month, more evaluations of the tick life cycle are necessary.

Analogous to other similar studies, the effect of climatic factors on the enhancement of the model's accuracy was clear in this study. In a study conducted in Turkey in 2007, monthly temperature was proposed as the predicting variable for cases of CCHF.[13] In 1998, having conducted temporal and local modeling of Lyme disease in England – a disease transmitted via Ixodes ticks – it was revealed that temperature and relative humidity were good predictors of the risk of the disease.[26] With temporal and local modeling of tick-borne encephalitis between the years 1993 and 1998 in Lithuania, it was revealed that climatic variations were good predictors of variations of this disease.[27]

As there is evidence of infection in Afghanistan and Pakistan,[28,29] our model demonstrated that in the years with more frequent livestock import from those two countries, the incidence of the disease increased. With respect to possible infections among the livestock of these two countries, an increase in human infections is anticipated along with an increase in livestock import. One of the reasons behind the ascending trend of the disease in the years 2006 and 2007 could be an increase in livestock import during those years compared to previous years. Verification of this, demonstrated with this model, necessitates revisions in livestock import from those countries, and where import is absolutely necessary, careful quarantine rules and supervision should be undertaken. Due to the country's increasing demand for meat during certain months of the year and to control marketing and prices, the government should introduce further quarantine restrictions and strict legal regulations for live livestock import, pertinent to the needs of the country.

As illustrated in Figures 2 and 3, although the model was able to make a distinct prediction of the disease incidence in most years, it was unable to predict the outbreak in late 2002. Although we were unable to predict this outbreak using our model's variables, such an outbreak could be related to an increase in migration of infected Afghans, as out of the 46 Afghan cases reported from Zahedan and Zabol during the eight years, 26 (56%) occurred in the year 2002. Over recent decades, Afghan migration to neighboring countries has increased due to internal warfare and insecurity,[30] and almost 10% of residents in Zabol and Zahedan are Afghan. It should be noted that there is no clear information about the current status of the disease in Afghanistan due to war, internal affairs, and poor health systems, but occasional reports are suggestive of a potentially high infectious rate in that country.[28,31]

In our model, there is an interval of 1 month for decision-making with respect to an early warning system, preventive programs such as the use of livestock insecticide sprays, improving quarantine programs, or even placing an absolute ban on livestock import.

We faced several limitations in this study. Some of them were related to the study design, which was conducted on surveillance system data; this study was considered a secondary one, hence we were limited by the available data, which will influence the credibility of the models and analyses. For instance, the city where treatment was taking place might have been registered in error, instead of the city of residence, or some patients might have acquired the disease after travelling to other areas, so some of our data used in the model may not be valid. Entomological data (tick fauna, prevalence, biology, etc.) could have an effect on the validity of the model to predict future CCHF scenarios; however these data were not available for inclusion in the current model.

The results of this study could be applied to improve the methods to control the disease and its surveillance. It is recommended that the authorities involved in the disease surveillance system update the model annually with new data to ensure improved prediction for the following years, in addition to increasing its credibility. The results of this study also showed the efficacy of predicting models and their development for early warning systems in Iran and other countries in the Middle East with the same epidemiological pattern, and suggest they are to be highly recommended.

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Conflict of interest: The authors declare that they have no conflict of interest.

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