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Original Article

Temporal Modeling of Crimean-Congo Hemorrhagic Fever in Iran

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Introduction: This study was aimed to investigate the effects of risk factors, and environmental and climatic factors affecting the occurrence of Crimean-Congo Hemorrhagic Fever (CCHF) in Iran. We used temporal modeling to predict the future occurrence of the disease in the country. **Methods:** We analyzed the data of 165 CCHF patients from all over Iran (except the districts Zabol and Zahedan in Eastern Iran) during 2000 to 2006. In this study, 130 districts with at least one reported case patient, and 780 districts with no reported case patient, as the control group, were included in the model. Logistic regression was used to design the temporal model of the disease at the district-month level nationwide with the purpose of predicting the occurrence of CCHF disease within one month in a district. **Results:** The designed model indicated that the history of previous reports of the disease in a district increased the risk of further reports of the disease (odds ratio: 2.53 (95% CI: 1.61, 3.97), (P<0.001)). Moreover, with each one-million increase in the urban population, the odds of a report of the disease increased 20% (P=0.003). The odds of the occurrence of the disease were reduced by 9% with the increase in each degree of latitude (P=0.028). The odds of the occurrence of the disease increased 6.25 times with the increase in each kilometer of altitude (P<0.001). The disease had a decreasing secular trend so that the occurrence of the disease was reduced by 10% each year (P=0.008). **Conclusion:** Our findings showed that based on the history of CCHF in districts, and population and geographical features, hot zones may be defined with some acceptable accuracy. *J Med Microbiol Infec Dis, 2014, 2 (1): 28-34.*

Keywords: Hemorrhagic Fever Virus Crimean-Congo, Iran, Temporal Modeling.

INTRODUCTION

Crimean-Congo Hemorrhagic Fever (CCHF) is viral zoonotic disease; the CCHF virus usually infects domestic and wild animals without any particular clinical symptoms. Humans are considered accidental hosts and the infection transmission usually occurs by tick bite or following contact with the blood and secretions of infected vertebrates. Farmers and those in contact with infected live stock and ticks are at higher risk infection. The average case fatality rate for this disease is about 30% [1, 2].

The geographical distribution of the virus is similar to that of its tick vectors. CCHF has been reported from over 30 countries in Africa, Asia, and Eastern Europe. Isolation of the virus and clinical disease in human have been reported from all the countries neighboring Iran [2-4]. In Iran, anti-CCHF virus antibodies in sheep and cattle were first detected in 1970 [5]. Numerous serological and molecular studies conducted later indicated the presence of antibodies against CCHF virus in humans and livestock, and the virus itself in ticks and humans across the country. However, the disease was neglected from 1978 due to the lack of attention and appropriate diagnostic methods [6]. The first clinical case of the disease was confirmed in 1999 and more cases have been reported from various parts the country since then.

In Iran, disease transmission is commonly via exposure to blood or viscera of infected livestock, or tick bite [7].

According to the National Notifiable Diseases Surveillance System, a probable CCHF case is a patient with one of the epidemiologic indicators and laboratory findings compatible with CCHF including thrombocytopenia (platelet count lower than 150,000 per ml) along with leucopenia (WBC lower than 3000 per ml) or leukocytosis (WBC higher than 9000 per ml). Confirmation of probable cases of CCHF is done in the Arboviruses and Viral Hemorrhagic Fevers Laboratory of the Pasteur institute of Iran (National Reference Laboratory), and is based on detection of specific IgM antibodies or 4-fold rise in the titer of IgG antibodies, or detection of viral antigen by reverse transcriptase PCR (RT-PCR), which is performed on the serum samples of probable CCHF cases sent to the laboratory [8].

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The main vectors of the virus are different species of ticks, particularly members of the genus *Hyalomma*, of which 31 different species have been identified and the majority of them can be found in Iran. The most prevalent species of *Hyalomma* in Iran is *Hyalomma anatolicum anatolicum;* the activity of this species begins in early spring and continues until mid summer and then reduces [9].

In order to determine and design appropriate methods for control and eradication of infectious diseases, the pathogens, the hosts and the environmental factors that affect the diseases should be studied. The climatic, environmental and geographical factors are integrated in the new surveillance systems for predicting the disease occurrences [10].

Geographical and seasonal distribution of many infectious diseases (especially vector-borne diseases) depends on the climate status and changes in temperature, humidity and precipitation. It is therefore necessary to have information on both reported cases of these diseases and climatic status of the regions over a period of time in order to demonstrate these associations and to simulate them [11]. Appropriate models can be useful for choosing the most effective techniques to prevent and control the diseases, and also to increase the understanding of the life cycle of infectious disease agents [12].

With increasing demand for effective disease early warning systems (EWS) and recent advances in enhancing the quantitative and qualitative climatic and environmental data, the use of effective EWS based on climatic and environmental factors is increasingly taken into consideration by international health organizations, and the surveillance systems are established based on these factors [13]. A study conducted in southeastern Iran revealed that temporal modeling may be useful in a CCHF early warning system [14].

Environmental and climatic changes play an important role in the occurrence of CCHF in humans; understanding of this issue, modeling, predicting the future occurrence of the disease and undertaking appropriate management actions can reduce the human casualties and economic losses. Therefore this study investigates the environmental and climatic factors affecting the occurrence of CCHF in Iran using temporal modeling.

MATERIALS AND METHODS

The study area. Considering that over 60% of CCHF patients in Iran have been reported from two eastern districts of Zabol and Zahedan, and are probably resulted from the import of livestock from Afghanistan and Pakistan, the pattern of disease occurrence in these two districts is different from the rest of the country. Hence, the model in this study was designed for the entire country except for these two districts. A separate model was designed for the two above-mentioned districts designated as Sistan model [14].

Iran is located in southwest Asia and shares land borders with Armenia, Azerbaijan and Turkmenistan in the north, Afghanistan and Pakistan in the east and Turkey and Iraq in the west.

It also shares water borders with Kuwait, Iraq, Saudi Arabia, Bahrain, Oman, Qatar and the United Arab Emirates through the Persian Gulf and Sea of Oman. The average altitude of Iran is over 1000 meters above sea level. This geographical location and being far from big seas have made Iran’s climate dry. However, Iran has a variety of different climates due to the great extent and presence of geographical features such as high altitudes, extensive low altitude lands and being adjacent to the Caspian Sea, the Persian Gulf and Sea of Oman, each influencing a separate climate zone. The average annual temperature of the country is about 18°C. In southern regions, despite the wet weather throughout the, the average temperature is even higher.

Methods. This study uses data from human samples with CCHF disease who were referred to the Arboviruses and Viral Hemorrhagic Fevers Laboratory of the Pasteur Institute of Iran (National Reference Laboratory). The required data such as gender, occupation, location (district and province of residence) and date of disease (day, month and year) were obtained from the confirmed human patients’ files. The data were validated by comparing with those case patients available in the Centre for Communicable Disease Control at the Iranian Ministry of Health and Medical Education. The months and years of the disease report were used for temporal modeling.

In order to design the temporal model, the climatic variables including: minimum, maximum and average temperature, precipitation levels and relative humidity during different months of the studied years in different districts; history of reported CCHF cases, latitude, longitude and altitude of the districts; human population and livestock (sheep and cattle) population density and the date of disease occurrence during the studied years were extracted and entered into the model as independent variables. To determine the seasonal trend of the disease, the sinus and cosine of the time (month) were calculated and entered into the equation as independent variables. A lag time ranging from 1 to 6 months was used in this model.

To create the maximum variance in the dependent variables of the model, a diverse group with negative outcome was entered into the model and in this regard, a case control design was used. In this study, 130 districts with at least one reported CCHF case during one year, and 780 districts with no history of CCHF during the study years, as control, were entered into the model. In each year, the control districts were randomly selected from the districts with no reports of the disease.

Given that the number of disease cases in a district-month was mostly one or zero, multifactorial logistic regression was used to design the temporal model of the disease. The backward stepwise likelihood ratio method was used to build the model. The Variables with a significance level less than 0.1 in the crude univariate logistic analysis were entered into the multifactorial logistic regression. The Variables with a significance level of less than 0.05 were considered significant. The Nagelkerke R^2 values of the independent variables remaining in the model were calculated.

This model was developed using the data obtained during 2000 to 2006 and its goodness of fit was analyzed using the data from 2007. After designing the model, the predicted probability value variable and the dependent variable were used to obtain the area under the receiver operating characteristic curve (ROC).

In order to find the most appropriate model, the effect of each variable and cluster of variables on the goodness of fit of models was explored in different formats, and the results were presented in the most logical way.

Multilevel modeling was used to identify the hierarchy structure in the data set and to specify the cluster effects in the model.

SPSS software (version 16, SPSS Inc.) was used for the data analysis. A logistic regression model with a 95% confidence interval was used to examine the association between each of the different climatic and geographical variables and the occurrence or non-occurrence of the disease in each year in various districts. The adjusted odds ratios were estimated to investigate the effects of covariates on the occurrence of CCHF.

RESULTS

From 1999 to 2007, 433 confirmed CCHF patients were diagnosed in Iran, of which 165 cases (38.10%) were included in the national model (patients from the entire country except the districts of Zabol and Zahedan). In the national model, 64.24% of the patients were male and the mean age of the patients was 33.49 (SD=1.67) years. The most probable confirmed cases of the disease were in the years 2001 and 2002, and the least in 1999. Most of these patients were butchers and slaughterhouse workers (n=36, 21.81%), housewives (n=34, 20.60%) and farmers (n=24, 14.54%). The case fatality rate of the disease during 1999-2007 was 27.2%.

The univariate analysis showed that the longitude and latitude of the district were important factors affecting the occurrence of the disease in a district.

This analysis also showed that the occurrence of the disease in densely populated cities was higher than other cities. The average population of districts with at least one positive human case during this period was 495,240 and the average population of districts with no reports of the disease was 167,295.

During this period, the probability of occurrence of the disease was higher in the districts with higher average annual temperatures (maximum, minimum and average) and lower annual precipitation and relative humidity, *i.e.*, in the more arid districts (Table 1). There was a significant difference in the amount of annual precipitation between districts with reports of CCHF and districts with no reports of disease; the average annual precipitation was 267 mm in districts with reported cases and 334 mm in control districts (P = 0.04).

Each of the explanatory variables was individually entered into the model using multifactorial logistic regression, and their effect was recorded using R^2 model. Eventually, after eliminating the variables whose effect was not statistically significant, 10 independent variables remained in the model. A Nagelkerke R^2 of 0.109 was obtained in the final model (Table 2).

The value for the area under the receiver operating characteristic curve (ROC) was calculated to be 0.775 (95% CI: 0.733, 0.816). The best sensitivity (82.34%) and specificity (70.65%) was found at the point 0.0185 (Figure 1).

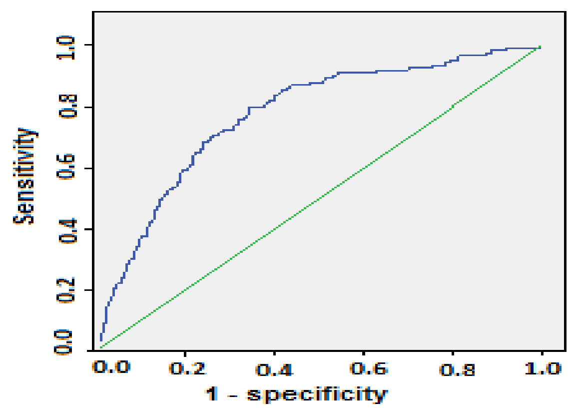

Fig. 1. Receiver operating characteristic curve (ROC) of the logistic regression model for predicting the occurrence of CCHF disease in a particular month in a district

The multifactorial logistic regression model showed that the risk of disease occurrence in districts with history of CCHF was nearly 2.5 times more than other districts. Also, the risk of CCHF occurrence was higher in the populated districts, so that each one-million increase in population increased the odds of disease by 20 percent. The disease was seen more often in districts with lower latitude and closer to the equator than in other districts.

Table 1. Results of univariate logistic analysis between independent variables used in the model and the occurrence of CCHF in each year in various districts

Variable	Unadjusted odds ratio (95% CI)	p-value
Longitude (scale)	1.08 (1.03, 1.14)	0.002
Latitude (scale)	0.86 (0.80, 0.92)	<0.001
Population (million subject)	1.27 (1.05, 1.52)	0.01
Mean of maximum annual temperature	1.09 (1.04, 1.14)	<0.001
Mean of minimum annual temperature	1.08 (1.03, 1.12)	<0.001
Mean of annual temperature	1.10 (1.05, 1.15)	<0.001
Annual precipitation	0.99 (0.98, 0.99)	0.04
Relative humidity	0.99 (0.98, 0.99)	0.04
Altitude (km)	0.80 (0.59, 1.09)	0.07
Livestock population density (with the unit of 1000 animals)	0.98 (0.93, 1.03)	0.37

Table 2. R^2values of multifactorial logistic regression for different models

Model number	Explanatory variable	Nagelkerke R^2
1	History of reporting CCHF in past years	0.036
2	Model 1 + Population (million subject)	0.040
3	Model 2 + Latitude (scale)	0.049
4	Model 3 + Year of reporting the disease	0.053
5	Model 4 + Seasonal variation	0.088
6	Model 5 + Altitude (km) and its square	0.090
7	Model 6 + Maximum temperature with 3 months delay	0.091
8	Model 7 + Relative humidity with 2 months delay	0.109

Table 3. Odds ratios and their confidence intervals for the explanatory variables of the multivariate logistic regression model in the Iran CCHF pattern

Explanatory Variable	Adjusted odds ratio (95% CI)	p-value
History of CCHF report	2.53 (1.61, 3.97)	<0.001
Population (million subject)	1.19 (1.06, 1.33)	0.003
Latitude (scale)	0.91 (0.83, 0.99)	0.028
Altitude (km) and its square (km^2)	4.52 (3.25, 5.79)	0.003
Year[a]	0.90 (0.81, 0.99)	0.008
Seasonal variation	3.13 (2.29, 4.28)	<0.001
Relative humidity with 2-month lag time	1.04 (1.02, 1.05)	<0.001
Maximum temperature with 3-month lag time	1.09 (1.01, 1.16)	0.016

a: year of CCHF report minus 2000

Each one-degree increase of latitude reduced the odds of occurrence of the disease by approximately 9 percent. In this study, 36.3% of cases were observed at altitudes lower than 1000 meters above sea level, 59.7% at 1000-2000 meters, and only 4% at higher than 2000 meters. Altitude factor did not show any association with the occurrence of the disease in the univariate analysis, but after the addition of other variables, its effect became significant (*P*=0.001) (Table 3).

The addition of the linear effect of the year increased the accuracy of the model. The model showed that the disease had a secular trend during the study period, so that the odds of occurrence of the disease reduced by approximately 10% each year. Two years after the first report of CCHF in Iran *i.e*., the years 2001 and 2002, the number of confirmed cases of the disease reached its maximum value.

The model showed that the sine and cosine transform monthly, which represents the seasonal variation of the disease, *i.e*., predicts the temporal variation of the disease. In other words, the disease shows a seasonal pattern and is repeated at regular intervals. The number of disease cases is higher in the first 6 months of the year, when ticks are more active, compared to the second 6 months of the year (Figure 2).

By calculating the temporal phase, it was determined that the model has a 2-month lag time. In other words, the increasing trend of the cases in the model begins in early June.

In this model, the maximum temperature of three earlier months had a predicting role for the occurrence of the disease, so that 1°C increase in maximum temperature in three earlier months increased the odds of disease occurrence by 9 percent. Also, it was shown that a 1% increase in relative humidity in two earlier months increased the odds of occurrence of the disease by approximately 4 percent.

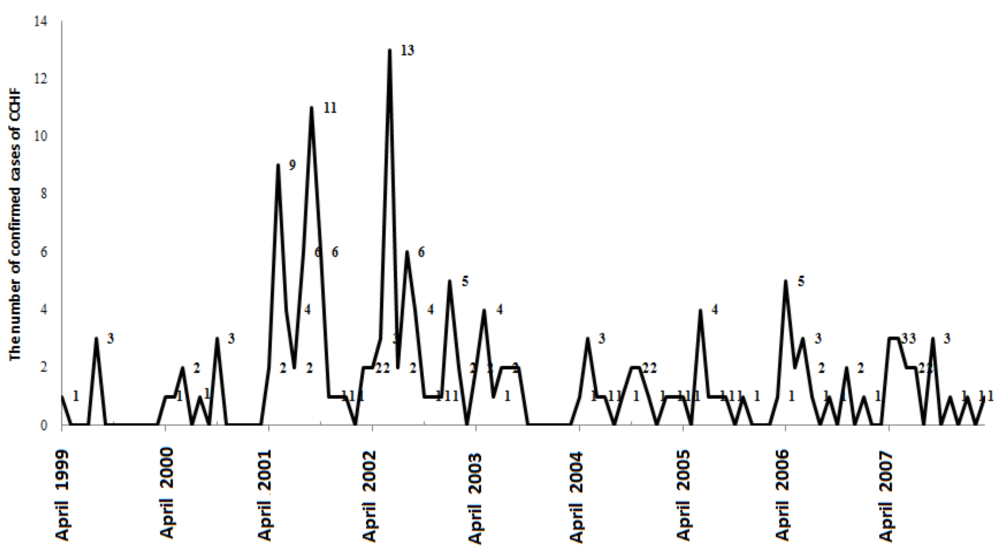

Fig. 2. The trend of CCHF reported during 1999 to 2007 in Iran

Our model predicted 10 out of 12 cases of the disease occurred in 2007 in various districts across the country in defined months. The model was also able to predict the 2 remaining cases in the defined districts, but could not predict the exact month of the occurrence. One of the cases occurred in Bandar Abbas, a district in southern Iran, in January, whereas the model had predicted the probability of occurrence of the disease between April and October 2007 in that district. The other case was reported in July 2007 in Najaf Abad, central Iran, while the model had predicted an occurrence of the disease in that district in May or June. Considering a 3-month confidence interval for the predicted months, all cases were predictable using this model.

DISCUSSION

In this study, the occurrence of CCHF was more probable in districts with higher average annual temperature, and lower annual precipitation and relative humidity. This finding is similar to other findings, which suggest that CCHF virus tends to be more active in dry regions [15]. Several studies have shown that increased temperature facilitates the hatching of the vectors that feed on the natural vertebrate hosts, accelerates the metabolic activity of vectors, and increases the tick bite rate [16].

Precipitation has an indirect effect on a vector's lifetime by affecting the relative humidity; low humidity creates suitable conditions for the growth of the vectors.

Precipitation and high humidity can have an inhibitory effect on vectors' population. In Europe and Asia, the desert, semi-desert, and steppe regions are known as favorable areas for the preservation and transmission of the CCHF virus [17-19]. Basically, ticks prefer to live in relatively dry climate [20], and this evidence is in agreement with the results of the raw analysis of this study.

Considering that the study on the disease foci indicated a correlation between disease cases in different years, this variable (the history of CCHF reports in past years) was entered into the model as an independent variable. Our model showed that the risk of CCHF occurrence in districts where the disease had previously been reported was nearly 2.5 times higher than in other districts. This confirms a correlation between cases of the disease in different years in a particular district. A part of this increased risk may be due to surveillance bias, *i.e*., in the districts with previous reports of CCHF, the health system is more alert for CCHF than in district without any previous reports.

The current model revealed that the risk of CCHF occurrence was higher in densely populated cities. These results are similar to the results of other studies on spatial modeling of CCHF in Iran, which indicates that most of the disease foci are found in densely populated areas [21].

The CCHF cases were detected more often in districts with lower latitude and thus closer to the equator than in other districts. As the model indicates, with every one degree increase in latitude, the risk of disease occurrence was reduced by nearly 9 percent. Our findings are similar to others studies, which suggest that the probability of disease occurrence increases in arid regions closer to the equator [2, 10]. Epidemiological studies in Africa revealed that CCHF virus distribution was mostly confined to the regions between the northern and southern tropical circles [22, 23].

In this study, longitude was not considered as a risk factor and this means that proximity to the eastern or western borders did not change the risk of disease occurrence. Accordingly, the numerous reports of the disease in recent years from eastern (Afghanistan and Pakistan) and western (Iraq and Turkey) neighbors, and official and unofficial livestock imports from these countries into Iran increase the probability that the virus circulating in Iran might have originated from these neighboring countries. Several articles have cited Afghanistan and Pakistan as the probable sources of the CCHF virus in Iran [14].

In this study, over 95% of disease cases were observed in districts with altitudes less than 2,000 meters above sea level. The model also showed that, like the majority of infectious diseases, the probability of disease occurrence reduces at high altitudes where the ideal conditions for growth and activity of ticks are not provided [24].

The addition of the linear effect of the year increased the accuracy of the model. The model showed that the disease had a secular trend during 2000-2006, so that the risk of CCHF occurrence was reduced approximately by 10% each year. Two years after the initial report of the disease in Iran, in the years 2001 and 2002, the number of probable and confirmed cases of the disease reached its highest rate. This could, in part, be due to the health system awareness and to the training conducted to familiarize the health officials with the disease nature after it was first reported in 1999 and 2000. In other words, the surveillance systems may have become more sensitive since 1999; more probable samples were tested and consequently, a higher number of confirmed cases and deaths were reported and proven. The number of confirmed cases has descended since 2002.

The model showed that the sine and cosine transform monthly, which represents the seasonal variations of the disease, predicts the temporal fluctuations of the disease. Simply stated, the disease showed a seasonal pattern, which repeated at regular intervals, with more occurrences in the warmer months and seasons of the year, while fewer cases in the colder months and seasons were expected. This seasonal pattern exists for majority of diseases transmitted by arthropods [25].

In this model, the maximum temperature of 3 months earlier had a predicting role for the occurrence of the disease, So that an increase of 1°C in maximum temperature of 3 months earlier increased the risk of CCHF occurrence by 9 percent. It should be noted that growth of ticks is faster in warm weather while they are inactive in cold weather [26]. In the northern hemisphere, the larvae of most *Hyalomma* species become active with increase in temperature in late winter and early spring [27]. In a study in Astrakhan, Russia, a significant correlation was observed between temperature decrease in winter and decrease in the number of CCHF cases in the next year [28]. Given that most cases of the disease in Iran have been found from mid-spring to mid-summer, a positive relationship between these cases and the temperature in 3 months earlier (mid-winter to mid-spring) was expected.

The humidity of the environment is an important and influential factor on various stages of the ticks' life cycle, *e.g.*, laying egg and hatching; also, choosing specific hosts and feeding on them is affected by the temperature and humidity of the environment [29, 30]. Our results showed that with an increase of 1% in relative humidity 2 months earlier, the odds of disease occurrence increased about 4 percent. Further interpretation of this subject and the positive impact of the maximum temperature 3 months earlier, requires additional studies on the ticks' life cycle in Iran. Several studies have also shown that early diagnosis systems can be designed based on climatic factors without a full knowledge of the impact of climate on components of the disease transmission cycle [20].

Monthly precipitation was not considered as a risk factor in this study, but crude analysis showed that the amount of annual precipitation in the districts with reports of CCHF was significantly lower than districts with no reports. This finding is similar to the other findings which have shown that the CCHF virus tends to be active in dry areas [15].

The model could predict 10 out of the 12 cases of disease in 2007 in various districts across the country in a defined month. Our model also predicted the 2 remaining disease occurrences in the particular districts, but it could not predict the exact month for disease occurrence. So if we consider a 3-month confidence interval for the predicted months, all cases were predictable using this model.

In this study some factors, to some extent, might have affected the validity of our results: 1) some patients might had been residents of small towns or villages who travelled to larger districts for treatment but their original residence was not reflected in their files and, consequently, a misclassification bias is possible in this regard, 2) the population density can be an indicator of differences in the economic, social, and cultural and health status of its residents and these factors can be effective determinants of the occurrence of the disease, however, but in this study they are not entered into the model as separate independent variables due to lack of a reliable indicator for them, and 3) lack of sufficient information about other variables that may affect the occurrence of disease, such as distribution of CCHF infected ticks and information about the pesticides used in different districts during this period.

The results of this study can be used to improve the disease surveillance and control procedures. We recommend that the custodians of the country's disease surveillance systems update this model with new data each year; this can increase its validity and would predict the disease status in the upcoming years more efficiently.

Our findings showed that based on the history of CCHF in districts and the population and geographical features, hot zones can be defined with some acceptable accuracy. Our study showed the seasonal fluctuations of the disease and could predict the temporal fluctuations of disease. In other words, the disease has a seasonal pattern and is repeated at regular intervals. By calculating the temporal phase it was determined that the model has a 2-month lag time, which means that the increase trend of CCHF cases begins in early June. The seasonal pattern of the disease is associated with the climatic factors such as temperature, relative humidity and precipitation. The results of this study demonstrate the efficiency of predictive modeling. We recommended development of this model for early warning systems in Iran and possibly other countries in the Middle East, with similar epidemiological pattern for CCHF.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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