Original Article

Potential Effects of Climatic Parameters on Human Brucellosis in Fars Province, Iran, during 2009-2015

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What's Known

- Climate is one of the important factors in the distribution of pathogenic agent, vector, and transmission environment.
- The Pathogen's and the host's environment, development, and survival strongly depend on climatic factors. Climatic parameters can provide the required condition for the survival of brucellosis.

What's New

- The effect of climate on brucellosis has been investigated using a scientific method.
- The findings of the present study can be used to prevent and reduce the incidence of the disease at similar locations.

Abstract

Background: Human brucellosis is widespread in Fars province. The present study aimed to investigate the effect of climate on its incidence and determine the areas prone to the infection.

Methods: Monthly meteorological data and the incidence rate of human brucellosis during 2009-2015 were collected and their correlation was studied using Pearson's correlation coefficient. Additionally, the multiple regression method and multi-layer perceptron neural network model were used to predict the incidence of human brucellosis. In order to analyze the data SPSS software (version 16.0), MATLAB software (version 8.1), and GIS software (version 10.4) were used.

Results: Pearson's regression analysis, on a monthly basis, showed a significant indirect correlation between the incidence of human brucellosis (with a time lag of up to 5 months) and climatic parameters (minimum temperature: -0.72 and evaporation: -0.73) in Abadeh (Fars, Iran). Moreover, there was a significant direct correlation ($P<0.001$) between the incidence of human brucellosis and the maximum relative humidity (+0.67) and rainfall (+0.48). The incidence of human brucellosis in Abadeh was predicted by using artificial neural network models (4 layers, 4 neurons in each layer), the Levenberg-Marquardt training algorithm, and Sigmoid transfer function. It was determined that a correlation rate of 0.89 in the training level and 0.8 in the test level (with the lowest error rate) were the best values in multi-layer perceptron modeling.

Conclusion: Climatic parameters are important factors in determining the incidence rate of human brucellosis in Fars province. Climate conditions provide a favorable environment for the spread of human brucellosis in this area.

Introduction

Brucellosis is a prevalent disease spreading from animals to humans (zoonosis). Brucellosis is still a major health problem in many countries across the world, including Iran. In humans, it usually causes weakness, faintness, fever, weight loss, and perspiration.[1] Brucellosis is highly contagious and affects the health of both humans and animals.[2] It can be directly transmitted to humans through contact with animals carrying the pathogenic bacteria Brucella, or indirectly through the consumption of

non-pasteurized dairy products and infected meat.[3] The disease is more prevalent in the Mediterranean countries (Portugal, Greece, Italy, Spain), the Middle East (Saudi Arabia, Israel, Iraq, Kuwait, Iran), and Latin America (Argentina, Peru, Mexico).[4, 5] Studies on human brucellosis in Iran during 1991-2008 showed that the provinces Khorasan, West Azerbaijan, Hamedan, Lorestan, Fars, East Azerbaijan, Kermanshah, Chaharmahal-o-Bakhtiari, and Markazi are the most infected regions.[6] In Iran, Brucella melitensis has the highest prevalence among the different types of Brucella.[7]

Climate is one of the important factors in the distribution of pathogenic agent (pathogen), vector (the mediator host carrying the pathogen), and transmission environment.[8] The Pathogen's and the host's environment, development, behavior, and survival strongly depend on climatic parameters. Temperature (in all seasons), moisture, and rain are the most effective factors. Other factors such as wind and sun hours can be significant too.[9] Brucellosis bacteria can survive in the environment for a long time.[10] Hence climatic irregularities, altering temperatures, and humidity can provide the necessary conditions for the survival of brucellosis.[11] Nevertheless, these factors have often been neglected in research studies despite the significance of brucellosis.[12]

Some diseases spread in certain geographical areas and are affected by the climatic conditions of that area. Such environmental parameters affect the genesis, exacerbation, and spread of the disease in various ways. Geographical factors associated with the spread of the disease are latitude, precipitation, relative humidity, and wind. In this regard, Alfonso Morales[12] studied the relationship between the Oceanic Nino Index (ONI) and the incidence of brucellosis in four regions of Latin America. The high number of brucellosis that occurred in El Nino years (warm seasons) had a significant relationship with the ONI index.[13] Various studies investigated the effect of global climate change on the transmission of infectious diseases[14] and the effect of climatic parameters on the incidence of airborne infectious diseases.[15] However, few studies have been conducted on the effect of climatic parameters on brucellosis. In Iran, many studies have been conducted on human brucellosis; however, the majority were medically oriented[1, 16] and only a few investigated the climatic effects.

Mohammadi studied the relationship between climatic parameters and the incidence of brucellosis in Isfahan, using the SPSS and GIS software packages, and constructed a zoning map of human and animal brucellosis.[17]

Entezari and Sepahvand studied the effects of temperature, rain, and elevation on brucellosis in Lorestan province. They concluded that an increase in the elevation and a decrease in the average temperature during the three coldest months of a year were associated with higher incidence of brucellosis.[18] Artificial neural networks (ANNs) learn from standard data and capture the knowledge contained in the data. ANNs are widely used in medical applications and various medical disciplines for modeling and clinical research.[19]

Considering the financial burden and physical damages caused by this disease, it is necessary to study susceptible geographical areas in order to control and prevent the disease. Climate is one of the most important factors that affect human health, especially in the presence of infectious diseases. Pathogen, host, and the transmission environment are the three main parts of infectious diseases. Some pathogens are transmitted through the host or need a mediator host to continue their cycle. A favorable climate condition is very important for the survival, reproduction, distribution, and transmission of the pathogen and the host.[13] Many studies have been conducted on pathogens and hosts,[14, 20] but only a few have considered the effect of climate on the incidence of brucellosis.

Despite the high rate of human Brucella and the endemic nature of this disease in the Fars province, previous studies on epidemiologic Brucella[21, 22] have not addressed the effective factors influencing its prevalence. Consequently, the present study aimed to investigate the incidence of brucellosis in different months and seasons, to find the effective climatic parameters, to predict the incidence of human brucellosis, and to determine its spread through Fars province. The findings of the present study allow prediction, control, and prevention of the disease. The practical goals of this research were (i) to identify the optimum climate conditions in the province for the incidence of human Brucella disease and (ii) to make an effective use of the educational and preventive programs in the susceptible areas.

Materials and Methods

Fars province has an area of about 133,000 square kilometers (8.1% of Iran) and is located at longitude 27°2' to 31°42' north and latitude 50°42' to 55°38' east.[23] It neighbors Isfahan province to the north, Kerman and Yazd provinces to the east, Hormozgan province to the south, Bushehr province to the west, and Kohgiluyeh

and Boyer-Ahmad province to the northwest.[24] Studying its climatic parameters by principal component analysis showed that its climate - in descending order - has thermal, precipitation, and summer precipitation components. Based on cluster analysis, the four climatic regions in Fars province are (i) a southern warm and dry area with very hot temperatures, low precipitation, and summer precipitation conditions (Lamerd, Darab, Neiriz), (ii) a warm, semi-wet western region with hot, humid, and high rainfall conditions (Kazeroun, Farashband, Ghir-Karzin), (iii) a mild and humid central region with autumn and winter humidity and high rainfall conditions (Fasa, Shiraz, Estahbanat, Marvdasht, Sepidan), and (iv) a cold and dry northern region with cold and dry conditions (Eghlid, Bovanat, Abadeh, Khorambid).[25]

The information on the incidence of human brucellosis in the cities of Fars province during 2009-2015 was obtained from the data gathered by the Department of Contagious Diseases Prevention, Shiraz University of Medical Sciences, Shiraz, Iran. The data included incidences across all health centers and hospitals in both urban and rural areas. The data were categorized according to age, sex, the use of milk and dairy products, contact with livestock, date of symptoms' access, and date of clinical diagnosis of the disease through tests. Monthly meteorological data during 2009-2015 were obtained from the Fars Meteorological Center that included rainfall, number of rainy days, minimum/maximum/average temperature (°C), minimum/maximum/average humidity, days with freezing temperatures, sun hours, evaporation rates, and maximum daily rainfall.

The two aspects of human brucellosis are the commune period (incubation of the brucellosis) and the appearance date of the first symptoms. The incubation period is the time between the invasion of an infectious pathogen and the appearance of the first symptoms. Information on the incubation period allows a simple determination of the source of the infection and calculation of the epidemiological treatment period.[7] As long as there is continuous contact with the source of the infection, either through drinking raw milk or occupational contact, it is difficult to determine the exact time of contamination and consequently the length of the incubation period. The incubation period is predominantly 1 to 3 weeks, but sometimes even up to 6 to 17 months.[26] Although most infections seem to become apparent within two weeks,[27] the incubation period could be far longer and it could take months before the symptoms appear, especially in endemic areas where the disease

has a longer incubation period.[28] Hence it is important that a time-lag for the environmental factors is taken into account when studying the relationship between climatic parameters and the incidence of human brucellosis. Since Fars province is among the areas with the highest incidence rate of human brucellosis in Iran, we used a longer incubation period. In terms of the second aspect of human brucellosis (the appearance date of the first symptoms), clinical diagnosis of the disease is determined through tests. In the present study, the date of symptom appearance was taken prior to that of the clinical diagnosis. Because of the difficulty in diagnosing human brucellosis and determining the incubation period, we used the data of the first symptom appearance as the baseline for studying the relationship between the disease and the climatic parameters.

Data related to climatic parameters were initially collected monthly and seasonally, and subsequently adjusted to the data associated with the incidence of the disease. To ensure that the data were correct and valid, the Run test method was used for the assessment of the homogeneity of the data (SPSS software, version 16.0). Pearson's correlation analysis was used to study the effects of climatic parameters on the incidence of human brucellosis. Correlation analysis is a statistical tool for the determination of the type and grade of the relationship between two quantitative variables. The correlation coefficient shows the intensity and the type (direct, indirect) of the relationship.[29]

To study the incidence of human brucellosis in a definite month, in terms of the incubation period, its origin must be sought in the previous months. Therefore, we chose climate parameters as independent variables with a time lag of 1, 2, 3, 4, and 5 months and the incidence of human brucellosis as the dependent variable to evaluate the Pearson's correlation. After studying the relationship between the variables, multiple regression was applied to predict the dependent variable or the response (human brucellosis incidence) by the predictor or independent variable.[30] The most important indicator for determining the relationship between the variables is the correlation coefficient. When a significant relationship between two variables is found, the independent variables can be estimated using the dependent variables. A regression equation was used to estimate the incidence rate of human brucellosis. Upon establishing a relationship between data using the correlation model, an artificial neural network (ANN) was used for predictions. ANN allows to study processes related to different parameters

with different significance rates and provides a reasonable response.[31] The most important advantage of ANN, compared to other smart systems is its self-learning capability to learn from the environment. Self-learning means that network weight values are selected such that the network behaves as expected. For example, the predicted incidence rate of human brucellosis by the network together with the accepted error rate equals the true incidence rate of human brucellosis. Different algorithms can be used to develop self-learning ANN, of which the error back-propagation training method is the most important algorithm.[32] In recent years, due to the rapid development of the geographic information systems (GIS), spatial data analysis has received considerable attention and has played an important role in the field of environmental and socio-economic science. Meteorological measurements, such as temperature and precipitation, are essential in assessing the relationship between the environment and diseases in the population.[33] In the present study, using Arc GIS software, the relationship between the annual average of the climatic parameters in Fars province and the average incidence of human brucellosis during 2009-2015 was studied to determine the locations prone to the incidence of human brucellosis. The SPSS software (version 16.0) was used for the correlation and regression model, MATLAB software (version 8.1) for modeling a multi-layer perceptron model (MLP) and GIS software (version 10.4) for the location of human brucellosis.

Results

A total of 6,103 infected patients were identified in Fars province during 2009-2015. Among the cities in this province, the highest number of incidences was found primarily in Abadeh, Eghlid, Marvdasht, Shiraz, Neiriz, and Kazeroon (figure 1). Initially, the Run test was used to determine the randomness of the data. The data were considered "true" since the values were <0.001 (below 5%).

The relationship between climatic parameters and the incidence of human brucellosis was studied by determining their degree of correlation and time lags (significance level was set at $P<0.01$). The results, based on monthly analysis, in Abadeh showed a correlation between the incidence of human brucellosis (with a time lag of 5 months) and climatic parameters. The correlations for these parameters for Abadeh were: minimum temperature (-0.72), evaporation (-0.73), maximum relative humidity (+0.64), sun hours (-0.56), rainfall (+0.48), and rainy days (+0.35). The corresponding values for Eghlid were: minimum temperature (-0.6), evaporation (-0.58), maximum relative humidity (+0.47), sun hours (-0.52), rainfall (+0.38), and rainy days (+0.34). These values for Khorambid were: minimum temperature (-0.58), evaporation (-0.58), maximum relative humidity (+0.57), sun hours (-0.54), rainfall (+0.5), and rainy days (+0.45). For other cities of Fars province (Neiriz and Fasa), the time lag was 4 months. The correlations for Neiriz were: minimum temperature (-0.54), evaporation (-0.59), maximum relative humidity (+0.53), sun hours (-0.47), rainfall (+0.38), and rainy days (+0.39). These values for Fasa were: minimum temperature (-0.5), evaporation (-0.51), maximum relative humidity (+0.47), sun hours (-0.47), rainfall (+0.36), and rainy days
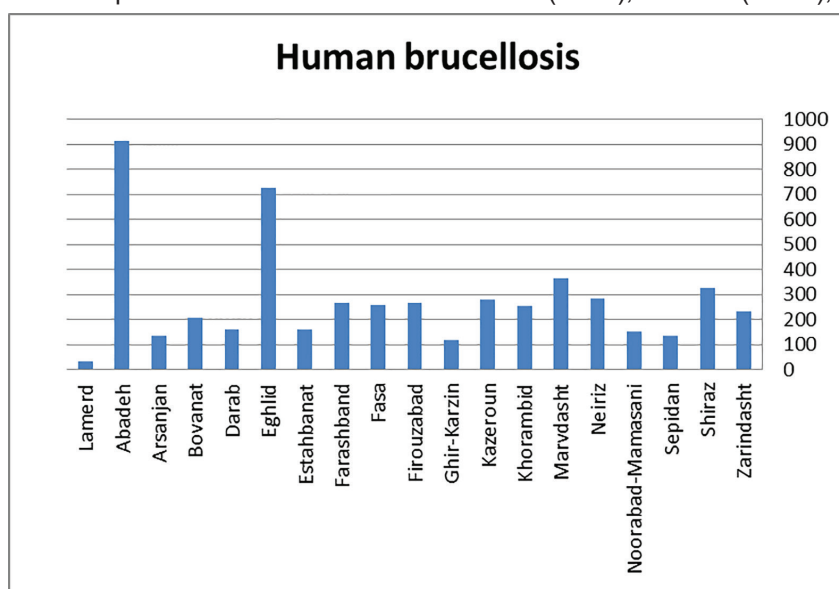

Figure 1: The figure illustrated the incidence of human brucellosis in Fars province.

(+0.39). The results of the remaining cities in the province are not mentioned due to the low level of correlation and the inefficiency of the model.

Pearson's correlation analysis on the seasonal basis was the same as those of the monthly analysis. The results of the relationship between the seasons and time lag showed that Neiriz and Fasa (1-season time lag) and Abadeh, Eghlid, and Khorambid (2 seasons time lag) had the highest correlation rates. It indicated a relationship between the incidence of human brucellosis and climatic parameters with 1 and 2 months delay, respectively (table 1).

The results of multiple regression models using the Enter method showed a significant value at <0.05 levels, indicating a significant relationship between the variables. Hence the linearity of the model was confirmed. The results of multiple regression models showed that evaporation, rainfall and rainy days, sun hours, average humidity, and minimum temperature with 4 and 5 months delay were the most

effective factors on the incidence rate of human brucellosis (table 2).

The inputs to the multi-layer perceptron network were evaporation, rainfall and rainy days, sun hours, average humidity, and minimum temperature with a 4 and 5 months delay for Abadeh, Eghlid, Khorambid, Neiriz, and Fasa. The optimal structure for this model was based on the number of layers, the number of neurons matching the highest correlation, and the least error in the test and error model. Abadeh was the best model in multi-layer perceptron neural network modeling with 4 layers, 4 neurons on each layer, the training algorithm of Levenberg-Marquardt, Sigmoid transfer function, a correlation rate of 0.89 in the train level and 0.8 in the test level, and the lowest error rate (table 3, figures 2 and 3).

In terms of location, the highest correlation rate between the minimum temperature and the incidence of human brucellosis was -0.455 indicating that the colder the area, the higher the

Table 1: Seasonal correlation rate between the climate factors and the incidence rate of human brucellosis in Fars province

Seasonal human brucella	Temperature	Min. temperature	Max. temperature	Relative humidity	Min. relative humidity	Max. relative humidity
Abadeh (lag 2)	-0.79**	-0.78**	-0.79**	0.67**	0.70**	0.75**
Eghlid (lag 2)	-0.63**	-0.62**	-0.63**	0.50**	0.54**	0.48*
Khorambid (lag 2)	-0.68**	-0.67**	-0.68**	0.65**	0.57**	0.68**
Neiriz (lag 1)	-0.48*	-0.47*	-0.48*	0.48**	0.45*	0.50**
Fasa (lag 1)	-0.55**	-0.53**	-0.54**	0.63**	0.56**	0.65**
	Evaporation	Sunshine	Rainfall	Rainy days	Freezing days	P value
Abadeh (lag 2)	-0.78**	-0.64**	0.54**	0.60**	0.40**	0.001
Eghlid (lag 2)	-0.69**	-0.53**	0.36*	0.39*	0.32**	0.001
Khorambid (lag 2)	-0.65**	-0.69**	0.53*	0.45*	0.35*	0.001
Neiriz (lag 1)	-0.46*	-0.42*	0.42*	0.49**	0.35*	0.001
Fasa (lag 1)	-0.50*	-0.59**	0.58**	0.52**	0.30*	0.001

*Significance at 0.05 level; **Significance at 0.01 level

Table 2: The results of monthly multiple regressions by the Enter model in Fars province

Monthly model	R	R-squared	Adjusted R-squared	P value
Abadeh	0.79	0.63	0.58	0.001
Eghlid	0.68	0.47	0.37	0.001
Khorambid	0.51a	0.26	0.11	0.001
Neiriz	0.56a	0.31	0.20	0.001
Fasa	0.57a	0.32	0.20	0.001

a: Predictors: evaporation, rainfall and rainy days, sun hours, average humidity, and minimum temperature with 4 and 5 months delay

Table 3: Results of monthly predictions of the incidence rate of human brucellosis in Fars province by multi-layer perceptron

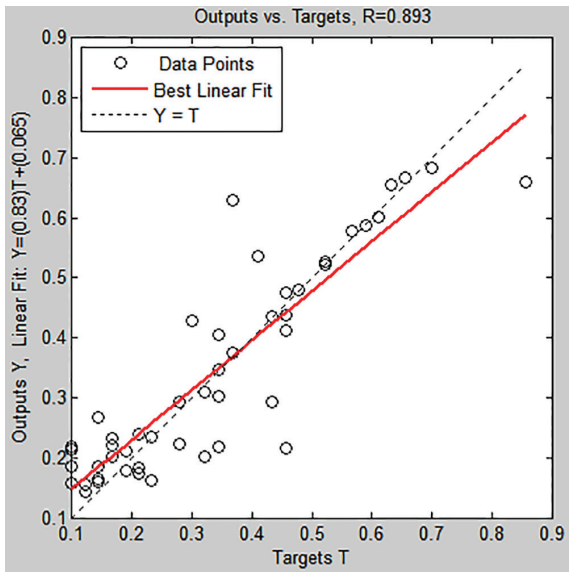| Monthly model		Train			Test			Network Structure
Model	Cities	R	NRMSE1	MAE1	R	NRMSE1	MAE1	
ANN1	Abadeh	0.89	0.21	0.26	0.80	0.35	0.34	4,4,4,1
ANN2	Eghlid	0.68	0.37	0.46	0.57	0.37	0.35	4,4,1
ANN3	Khorambid	0.79	0.28	0.43	0.59	0.44	0.35	8,1,2,1
ANN4	Neiriz	0.67	0.41	0.44	0.65	0.36	0.22	5,2,1
ANN5	Fasa	0.71	0.51	0.54	0.56	0.48	0.38	4,4,3,2

Figure 2: The correlation rate of 0.89 at the training level in Abadeh.
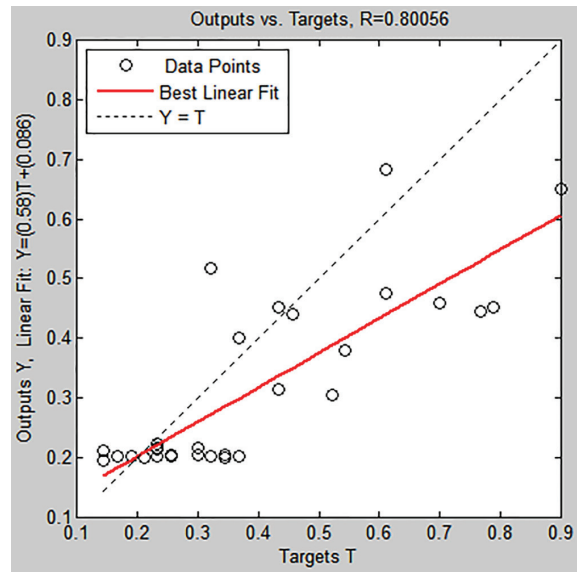

Figure 3: The correlation rate of 0.80 at the test level in Abadeh.

incidence rate. Cities such as Eghlid, Khorambid, and Abadeh with the highest elevation above the sea level, had a higher incidence rate of human brucellosis with a correlation rate of 0.481. Northern cities in Fars province with higher elevation and a lower temperature had a colder climate, allowing the bacteria to survive and

reproduce optimally (figures 4 and 5).

Discussion

Examining the relationship between climatic parameters and the incidence of human brucellosis on monthly basis showed that Abadeh
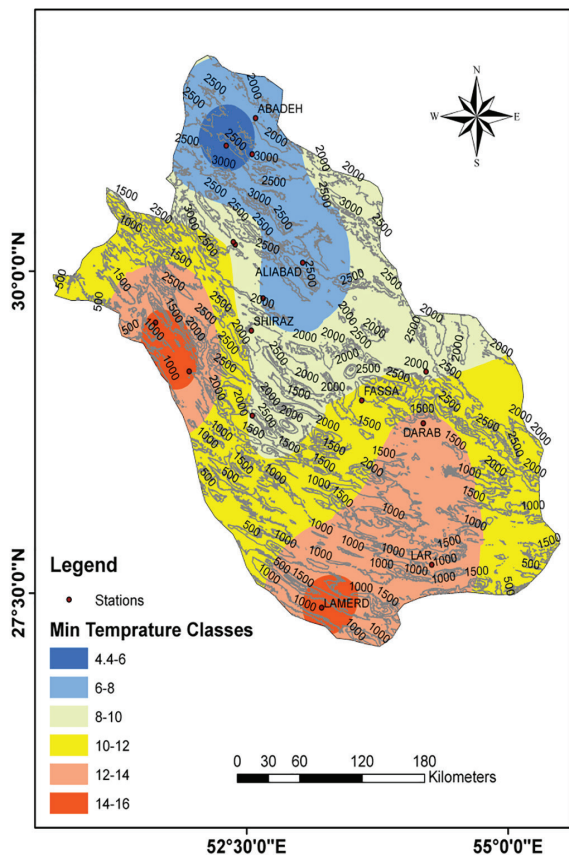

Figure 4: The zoning map of minimum temperatures in Fars province.
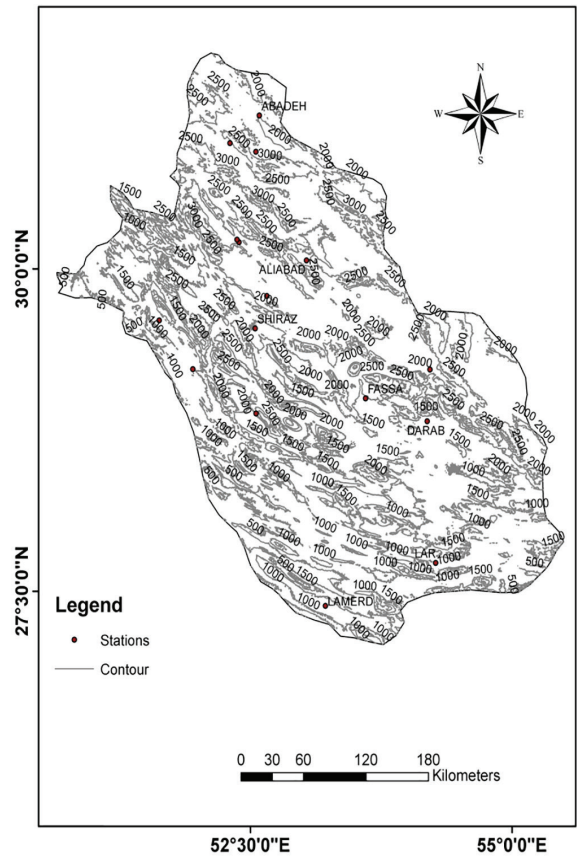

Figure 5: The zoning map of the elevations in Fars province.

had the highest incidence and correlation rate. It indicated that the incidence of human brucellosis had an inverse relationship with the temperature. The highest incidence rate of human brucellosis was observed at the lowest temperatures with a time lag of 4 and 5 months. The lowest temperatures in Abadeh were during the months of December to March and the highest incident rate of human brucellosis occurred during the months of March to July; corresponding to the incubation period. A decrease in the incidence rate during the months of September to March (winter and spring) was associated with the decreased activity of the brucellosis bacteria since high temperatures and low humidity reduced the activity of brucellosis to a minimum level. There was a positive correlation between the incidence of human brucellosis and humidity. Higher humidity levels caused a higher incidence of human brucellosis. Higher evaporation rates (i.e. drier air) also caused a lower incidence of human brucellosis. During warm months, as the sun hours increased the incidence of human brucellosis decreased. Higher amounts of rainfall and rainy days provided a better condition for the survival of the brucellosis bacteria and consequently a higher incidence of human brucellosis. Days with freezing temperatures also had a direct relationship with the incidence of human brucellosis (i.e. higher incidence).

Similar to our study, Farahani and colleagues,[30] Heshyani and colleagues,[34] and Hatami and colleagues[25] reported that the highest incidence rate of human brucellosis occurred in spring and summer. They believed that the reason for such seasonal high rate was due to increased contact with the remains from aborted pregnancies. It should be noted that they did not take into account the origin of human brucellosis in the previous months and thus excluded the average incubation period from their analysis.

Brucellosis is a disease with non-specific symptoms and possible delays in its diagnosis is normal even after the incubation period. In some cases, the incubation period lasts for months after the infection and the appearance of symptoms has a longer incubation period, especially in endemic areas.[29] Consequently, the study of the relationship between climatic parameters and the incidence of human brucellosis requires consideration of environmental factors with a time lag. We believe that the reason for the incidence of human brucellosis in these two seasons must be sought in the climatic conditions during the previous 4 or 5 months.

Alfonso[12] found that changes in temperature and humidity affect the survival of the bacteria.

In contrast with our findings, Mohammadi and colleagues[17] concluded that temperature had a direct relationship with the incidence of human brucellosis, which could be due to the exclusion of time lag in their analysis. For the incubation period, we applied Pearson's correlation and linear regression model and found that there was a relationship between the high incidence of human brucellosis and the cold seasons (i.e. lower temperatures and higher humidity levels provide better conditions for the survival of the bacteria and consequently higher incidence rate of human brucellosis).

Determining the inputs that affect the incidence of human brucellosis in the MLP model was an important factor for the proper performance of the network. In the present study, the climatic parameters (evaporation, rainfall and rainy days, sun hours, average humidity, and maximum temperature with a time lag of 5 months) that were used as inputs led to useful results. Abadeh had the highest correlation rate between climatic parameters and the incidence of human brucellosis as well as the lowest error in the MLP model. In addition to using the appropriate climatic parameters, the use of statistical methods (linear regression and ANN) was effective in predicting the incidence of diseases such as Brucella.

Sepahvand and Entezari[18] conducted a study in Lorestan province and showed a relationship between the incidence of human Brucella and an increase in the elevation and a decrease in the temperature during the three coldest months of the year. We also obtained similar results in Fars province. There was a higher incidence rate in cold and humid areas. Since many of the climatic parameters do not alter rapidly, there is a need for increased awareness about the disease and more education and training of the involved people such as farmers, livestock breeders, veterinarians, slaughterhouse staff, butchers, and livestock experts.

Conclusion

It can be generally stated that Fars province is one of the areas with the highest incidence rate of human brucellosis in Iran. Climate is one of the most important factors in the incidence of this disease. Abadeh and Eghlid, due to their climate, were the high-risk areas for the spread of the disease. Preventive actions are required in these cities during fall and winter. Colder and more humid areas had a higher incidence rate of human brucellosis. Statistical models such as multiple regression and MLP neural network model produced useful results and

provided a better understanding of the disease. Meteorological inputs can also be used to predict other diseases, like human brucellosis, when statistical methods such as multi-layer regression and ANN are applied. For a better performance, it is suggested to predict the incidence of human brucellosis by ANN. Additionally, symptoms should be used as inputs in the model along with climatic parameters.

Conflict of Interest: None declared.

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