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Establishment of an early warning system for cutaneous leishmaniasis in Fars province, Iran

Marjan Zare[1], Abbas Rezaianzadeh[2]✉, Hamidreza Tabatabaee[3], Hossain Faramarzi[4], Mohsen Aliakbarpour[4], Mostafa Ebrahimi[5]

[1]Department of Epidemiology, School of Health, Shiraz University of Medical Sciences, Shiraz, Iran

[2]Colorectal Research Center, Shiraz University of Medical Science, Shiraz, Iran

[3]Research Center for Health Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

[4]Department of Community Medicine, Medical School, Shiraz University of Medical Sciences, Shiraz, Iran

[5]Department of Communicable Diseases, Shiraz university of Medical Science, Shiraz, Iran

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ABSTRACT

Objective: To establish an early warning system for cutaneous leishmaniasis in Fars province, Iran in 2016.

Methods: Time-series data were recorded from 29 201 cutaneous leishmaniasis cases in 25 cities of Fars province from 2010 to 2015 and were used to fit and predict the cases using time-series models. Different models were compared *via* Akaike information criterion/Bayesian information criterion statistics, residual analysis, autocorrelation function, and partial autocorrelation function sample/model. To decide on an outbreak, four endemic scores were evaluated including mean, median, mean + 2 standard deviations, and median + interquartile range of the past five years. Patients whose symptoms of cutaneous leishmaniasis began from 1 January 2010 to 31 December 2015 were included, and there were no exclusion criteria.

Results: Regarding four statistically significant endemic values, four different cutaneous leishmaniasis space-time outbreaks were detected in 2016. The accuracy of all four endemic values was statistically significant (P<0.05).

Conclusions: This study presents a protocol to set early warning systems regarding time and space features of cutaneous leishmaniasis in four steps: (i) to define endemic values based on which we could verify if there is an outbreak, (ii) to set different time-series models to forecast cutaneous leishmaniasis in future, (iii) to compare the forecasts with endemic values and decide on space-time outbreaks, and (iv) to set an alarm to health managers.

1. Introduction

Some vector-borne infections like leishmaniasis follow space and time trends for which Early Warning Systems can be feasible and useful tools to find the potential outbreaks[1]. Early Warning Systems are alert systems to predict epidemic outbreaks in the region. In the 1910s, Capitain S.R. Christophers from British army set a system to predict malaria in India using climatic and socioeconomic data. Since then, it has been used as a helpful tool to aid poor disease-infected nations, make health policies, and manage services to the

✉Corresponding author: Abbas Rezaianzadeh, Colorectal Research Center, Shiraz University of Medical Science, Shiraz, Iran.
Tel: +09173150834, +98 713256007
Fax: +98 7137260225
E-mail: rezaiana@gmail.com
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infected areas.

Leishmaniasis represents the fourth most important neglected tropical disease, carrying the burden of almost 2.1 million infected people per year[2-4]. Leishmaniasis is a vector-borne protozoa disease. It is a parasitic infectious disease caused by genus *Leishmania* species transferred by infected Phebotomine sand fly bites. There are four main types of leishmaniasis, namely anthroponotic and zoonotic visceral leishmaniasis (VL) and anthroponotic and zoonotic cutaneous leishmaniasis (CL). Humans are supposed to be the only source of infection for sand fly vectors in anthroponotic types. In zoonotic types, animals are reservoirs that maintain and spread *Leishmania* parasites. The cutaneous type of *Leishmania* usually causes skin ulcers on open parts of body. It may bring about a great number of ulcers ending up in harsh disabilities and generate lasting ulcers, which can be a social stigma[5-11].

Generally, more than 350 million people are at risk of leishmaniasis in 88 countries around the world and nearly 12 million people are currently contaminated. Indeed, approximately two million new cases occur yearly among which, 500 000 cases are VL and the other 1 500 000 ones are CL. Moreover, nearly 90% of CL cases are located in Afghanistan, Algeria, Brazil, Iran, Peru, and Saudi Arabia[12-14]. CL is the representative of highly-prevalent diseases in Fars province, Iran that is known to be an endemic area[12]. Sand flies live in a large zone of Fars province, including Sepidan, Arsenjan, Neireez, and Estahban. In the last year, almost 6 000 cases were reported in Fars province among which, 2 000 cases occurred in urban and 4 000 in rural areas. The incidence rate of CL has been reported to be 106.01-144.00 cases per 100 000 inhabitants in Fars province, Iran[4].

In epidemiological and public health viewpoints, health status changes geographically and chronologically. Therefore, it could be helpful to detect areas with an accumulation of health problems. Modern technologies, such as Geographic Information System, have enabled us to do earth-based analysis and disease mapping in Early Warning Systems. In a previous study, the results of spatiotemporal analysis indicated that transmission of American CL followed a spatial and temporal pattern in Venezuela[11].

The current study aims to set a protocol for developing Early Warning Systems for CL in Fars province, Iran, considering CL as a space-time related infection. Early Warning System encompasses fitting time-series modes, then estimating and forecasting CL cases in 25 different cities of Fars province, and finally detecting the potential CL outbreaks in 2016.

2. Materials and methods

2.1. Study design

Time-series design, including 29 201 incidence cases of CL in Fars province from 2010 to 2015, was conducted to fit and predict CL cases in Fars province in 2016. The cases were registered monthly and obtained from hospital records. Akaike Information Criterion (AIC) is an estimator of the relative quality of statistical models for a given set of data. Given a collection of models for the data, AIC estimates the quality of each model, relative to each of the other models. Thus, AIC provides a means for model selection. Bayesian Information Criterion (BIC) is also a criterion used for model selection among a finite set of models. In this context, the model with the lowest BIC is preferred. It is based, in part, on the likelihood function and it is closely related to AIC. Auto correlation function (ACF) and partial auto correlation function (PACF) model/sample evaluate the conformity of the observed and fitted patterns in data. A variety of time-series models are normally applied and the best ones are selected based on the goodness of fit criteria, such as residual analysis, lower AIC/BIC statistics, and ACF/PACF conformity. There are seven tests included in residual analysis, each of which examines one presumption of white noise parameter. In this regard, a model with lower AIC/BIC is preferable showing lower divergence of the observed from the fitted values in time-series models. Finally, the more ACF, PACF model/sample matches, the better the model fits.

Four traditional endemic scores were considered as cutoffs for CL estimates during 2010-2015. These four cutoffs were the average of the past five years of CL cases, median of the past five years, the mean of the past five years plus two multiplied by standard deviation, and median of the past five years plus interquartile range (IQR). After fitting time-series models to estimate CL cases in 2010-2015, the accuracy of the cutoffs was assessed using Receiving Operating Characteristic (ROC) curves. The points with maximum sensitivity multiplied by specificity were considered as potential endemic values.

2.2. Study area

Fars province, with Shiraz as its capital city, locates in south of Iran, with an area of 122.661 km^2 (7% of the total area of the country). Geographically, Fars province is located on 27°3’ and 31°40’ northern latitude and 50°36’ and 55°35’ western longitude. This province is composed of 25 cities. In this study, the geographical coordinates of each city were found through Google-Earth (US Department of State Geographer 2016). The average temperature of Shiraz is 16.8 ℃ ranging from 4.7 ℃ to 29.2 ℃. Besides, its average altitude is 1 524 meters above the sea level[4].

2.3. Subjects

This study was performed on 29 201 confirmed CL cases. CL cases were recorded monthly. The cases were patients from 25 different cities of Fars province registered in the Contagious Disease Control center located in the main stance of School of Medicine, Shiraz, Iran. The cases who showed positive CL through smear, culture, or polymerase chain reaction, and showed symptoms of CL began from 1 January 2010 to 31 December 2015 were included in the study. All data were obtained from hospital records (clinical sheets) and there were no exclusion criteria. Indeed, there was no sample size calculation since all eligible patients were included in the study using census data. All ethical steps, including data collection and analysis as well as report of the results, were in accordance with the standards approved by the Ethics Committee of the Ministry of

Health, Treatment, and Medical Education (IR.SUMS.REC.1396.S755). Besides, the work process was completely anonymous and the results were reported to the study participants.

2.4. Population data

Clinical diagnosis of CL was obtained from the patients' medical records. Cases were recorded monthly from 1 January 2010 to 31 December 2015 for each city. The geographical coordinates for each city were obtained through Google-Earth based on the latitude-longitude coordinate system. Finally, the data were stored in Microsoft Excel 2007 and were exported to text format for further analysis.

2.5. Information processing

SPSS statistical software, version 22 was used for statistical analysis and ITSM 2002 software was employed for time-series modeling. In addition, maps of CL cases were generated in ArcGIS, version 10.

2.6. Statistical analysis

Median ± quartile deviation was used for continuous variables and minimum, maximum, relative frequency, bar charts, and frequency distribution tables were applied for qualitative variables. To testify the normality assumption, Kolmogorov-Smirnov test was used. In addition, *chi*-square test was utilized to assess the equal frequency of CL occurrence over time and place. Kruskal–Wallis test was also used to evaluate the equality of median of cases through different time periods and places. Significance level was considered to be 0.05 for all statistical tests.

Various time-series models were applied and the best ones were chosen to predict CL cases in 2016. At the end, the model with lower AIC/BIC, more concordance of ACF, PACF sample/model, and significant residual tests was chosen.

Various time-series models were used to predict CL cases in 2016 for 25 cities of Fars province from which just the results of Arsenjan and Firoozabad have been presented. For all models, seasonality of 12, linear or quadratic trend, and Box-Cox transformation were used. To evaluate the goodness of fit of every fitted model, residual analysis, AIC/BIC scores, and ACF, PACF sample/model were assessed.

3. Results

As the interpretation of the results of 25 cities is similar, two cities Arsenjan and Firoozabad among them are selected as representatives to show the results found in the study.

3.1. Interpretation of results for Arsenjan

To reach the stability of variance, Box-Cox transformation was set near zero. Based on the observed linear trend and the seasonality of 12, moving average (MA) (4) was fitted. The estimated CL cases during 2010-2015, predicted CL cases in 2016 (12 months), and ACF, PACF sample/model for Arsenjan are presented in Figure 1 and Figure 2, respectively.

In Figure 1, MA (4) was applied to estimate CL cases during 2010-2015. To assess the accuracy of endemic values, ROC curve procedure was used. Accordingly, all four scores were highly accurate with statistically significant area under ROC near 1. From the coordinate points of ROC results, the points with maximum sensitivity multiplied by specificity were chosen as endemic values.

Based on Figure 2, MA (4) could be a good model because many of sample/model correlations were matched in the graph (one or two non-overlaps are ignorable). The results of residual analysis for Arsenjan and Firoozabad are presented in Table 1.

AIC/BIC scores were estimated to be 212/219 and 212 for Arsenjan and Firoozabad respectively, also Order of Min AICC YW Model for Residuals estimated to be zero for both cities.

3.2. Interpretation of results for Firoozabad

To reach the stability of variance, Box-Cox transformation was set near zero. Based on the observed linear trend and the seasonality of 12, auto regressive (1) was fitted. The estimated CL cases during 2010-2015, the predicted CL cases in 2016 (12 months), and ACF, PACF sample/model for Firoozabad are presented in Figure 3 and Figure 4, respectively.

Based on different four endemic values for CL cases, the predicted time-series values of CL for the 25 cities of Fars province in 2016 (January to December) showed different epidemic outbreaks. The results are presented geographically in Figure 5. The months of outbreak occurrence are shown for each of the scenarios in Table 2.

For results of all other 23 cities not mentioned here, Auto Regressive Moving Average (ARMA), Auto Rregressive (AR), MA models with seasonality of 12, and linear or quadratic trend were applied. In addition, different smoothing methods encompass MA, Exponential, and Fast Fourier Transform (FFT) were done to extract the estimated values of CL cases in 2010-2015.

Table 1. Residual analysis results for Arsenjan and Firoozabad.

Test	*P* value	
	Arsenjan	Firoozabad
Ljung – Box	0.7	0.85
McLeod – Li	0.002	0.04
Turning points	0.19	0.92
Diff sign points	0.84	0.54
Rank test statistic	0.92	0.89
Jarque-Bera	0.6	0.92

Note: All test statistics are significant at 0.05 level for Arsenjan and Firoozabad. It is noteworthy to mention that if four out of the first six test statistics are statistically significant, it is enough to say that the model is a good fit, but the order of Min AICCYW Model for residual test needs to be zero. This test assesses the mean of white noise residual. The lower the AIC/BIC scores, the better the model fits. From the first six tests, just the second one (McLeod- Li) needs to be significant and the other five tests should be greater than or equal to 0.05, showing that the model is good based on residual analysis.

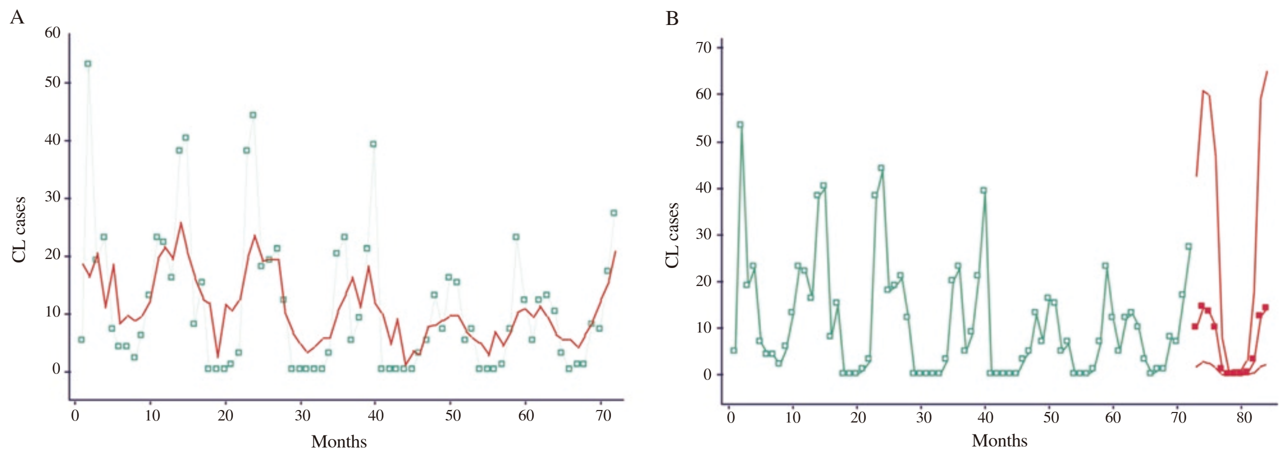

Figure 1. (A) Moving average (4) estimating the number of cutaneous leishmaniasis cases of Arsenjan during 2010-2015. The green dashed line represents the number of observed cutaneous leishmaniasis cases in 2010-2015. The simple red line indicates moving average (4) of the number of estimated cutaneous leishmaniasis cases in 2010-2015. (B) Predicted moving average (4) for cutaneous leishmaniasis cases of Arsenjan in 2016. The green line represents the predicted cutaneous leishmaniasis cases in 2010-2015. Red line represents predicted cutaneous leishmaniasis cases in 2016 with its confidence interval.

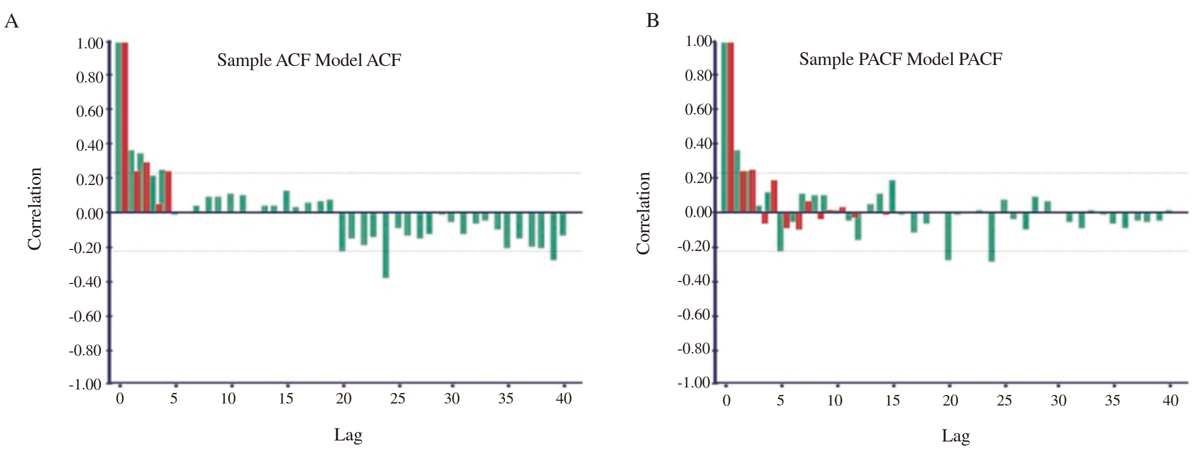

Figure 2. Sample/model moving average (4) of auto correlation function (ACF) (A) and partial auto correlation function (PACF) (B) for Arsenjan in 2016. The green correlations are derived from the sample and the red correlations are taken from the fitted model. Two dashed horizontal lines are confidence bands. A model is considered good in case the sample and model correlations out of the bands overlap.

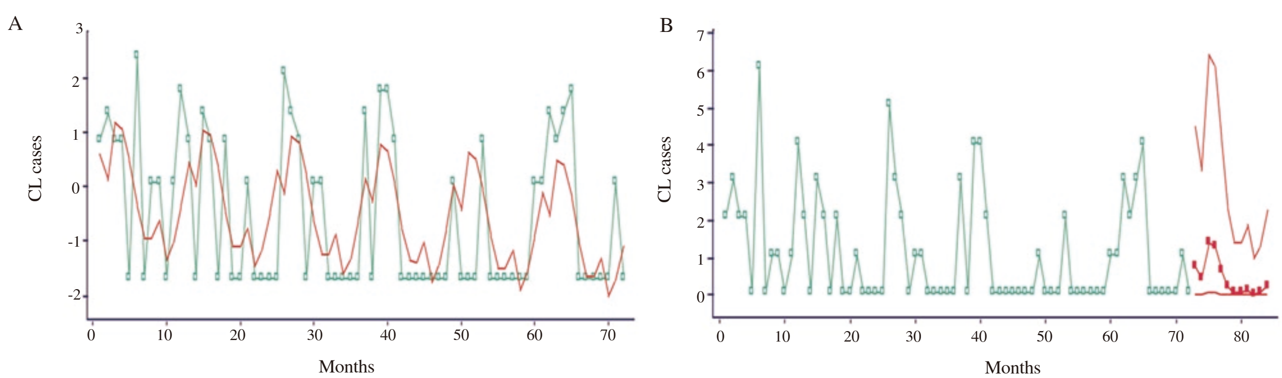

Figure 3. (A) Auto regressive (1) estimating the cutaneous leishmaniasis cases of Firoozabad during 2010-2015. The green dashed line represents observed cutaneous leishmaniasis cases in 2010-2015. The simple red line indicates moving average (4) of the number of estimated cutaneous leishmaniasis cases in 2010-2015. (B) Predicted auto regressive (1) for cutaneous leishmaniasis cases of Firoozabad in 2016. The green line represents the predicted cutaneous leishmaniasis cases in 2010-2015. Red line represents predicted cutaneous leishmaniasis cases in 2016 with its confidence interval.

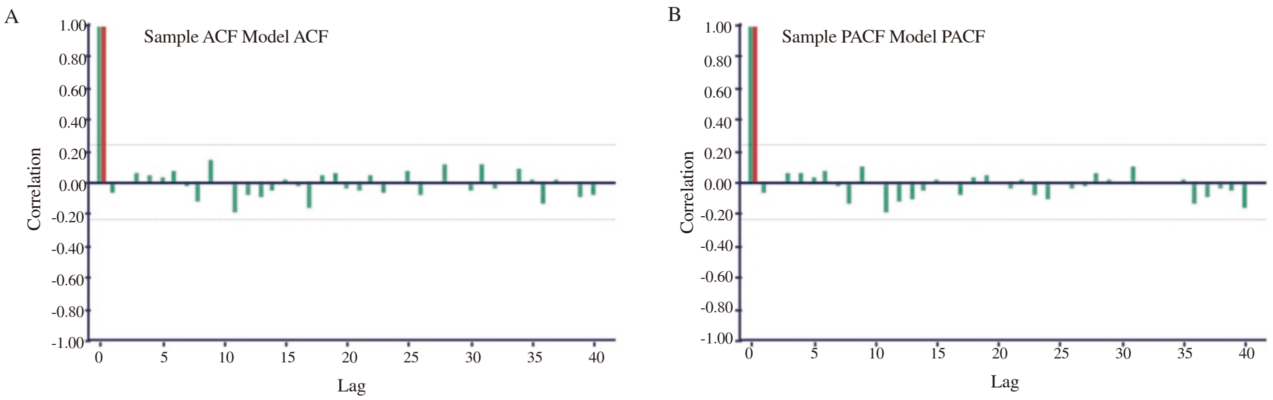

Figure 4. Sample/model auto regressive (1) of auto correlation function (A) and partial auto correlation function (B) for Firoozabad in 2016. The green correlations are derived from the sample and the red correlations are taken from the fitted model. Two dashed horizontal lines are confidence bands. A model is considered to be good if the sample and model correlations out of the bands overlap.

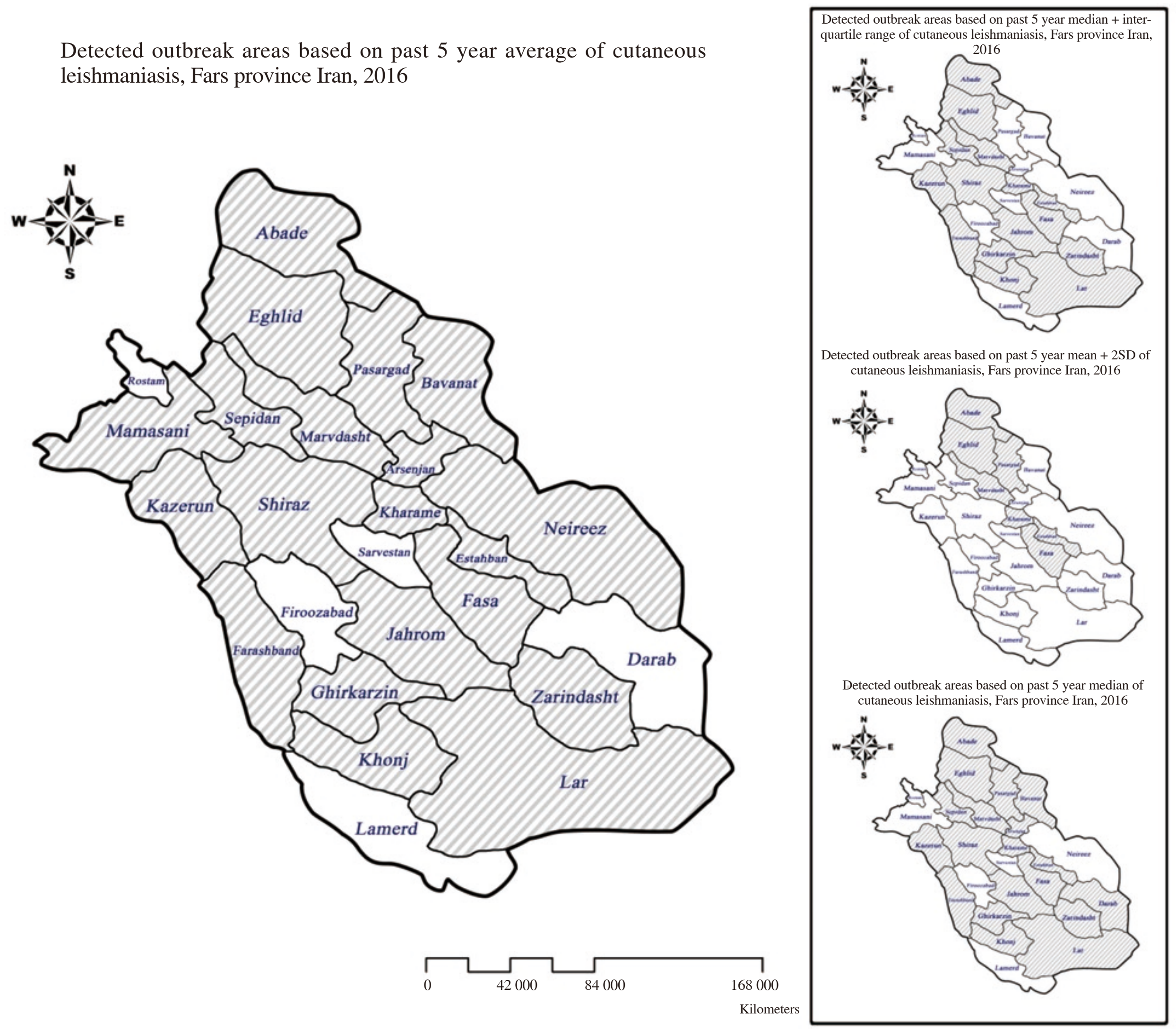

Figure 5. The detected epidemic outbreaks in Fars province, Iran in 2016 considering four different endemic scores. Dashes: outbreak areas. Simple white: endemic areas. Scale bar is the same for all 4 maps.

Table 2. Predicated months of detected outbreaks in 2016 according to different alarm systems.

Alarm systems	City	Month
Based on mean	Arsenjan	Aug, Sep, Oct, and Nov
	Zarrindasht	Jan, Sep, Oct, Nov, and Dec
	Stahban	Jan, Feb, Apr, Aug, Sep, Oct, Nov, and Dec
	Shiraz	Jan, Sep, Oct, Nov, and Dec
	Sepidan	Jan, Oct, and Nov
	Pasargad	Sep, Oct, Nov, and Dec
	Neireez	Jan, Nov, and Dec
	Marvdasht	Jan, Oct, Nov, Dec, Feb, Aug, and Sep
	Mamasani	Nov and Apr
	Lar	Jan, Oct, Nov, and Dec
	Khonj	Jan, Oct, Nov, and Dec
	Kharame	Jan, Oct, Nov, Dec, and Sep
	Kazeroon	Jan, Oct, Nov, and Dec
	Jahrom	Jan, Oct, Nov, Dec, Feb, Mar, Apr, Aug, and Sep
	Ghirkarzin	Jan, Nov, Dec, Apr, Aug, and Sep
	Fasa	Jan, Oct, Nov, and Dec
	Farashband	Oct, Nov, Dec, and Jun
	Eghlid	Oct, Nov, Dec, Aug, and Sep
	Bavanat	Oct, Nov, and Dec
	Abade	Jan, Oct, Nov, Dec, Feb, Aug, and Sep
Based on median + interquartile range	Zarrindasht	Jan, Sep, and Dec
	Abade	Jan, Oct, Nov, Dec, Aug, and Sep
	Stahban	Jan, Oct, Nov, Dec, and Sep
	Shiraz	Oct and Nov
	Sepidan	Oct
	Marvdasht	Oct and Nov
	Lar	Jan, Nov and Dec
	Khonj	Jan and Dec
	Kharame	Jan and Oct
	Kazeroon	Jan, Nov, and Dec
	Jahrom	Oct and Dec
	Ghirkarzin	Jan, Nov, Apr, and Sep
	Fasa	Jan, Oct, and Nov
	Farashband	Oct, Nov, and Dec
	Eghlid	Oct, Nov, and Dec
Based on mean + 2SD	Stahban	Nov and Dec
	Pasargad	Oct
	Marvdasht	Nov
	Kharame	Nov and Oct
	Fasa	Jan, Oct, Nov, Dec, Aug, and Sep
	Eghlid	Oct, Nov, and Dec
	Abade	Oct, Nov, Dec, and Sep
Based on median	Arsenjan	Jan, Sep, Oct, Nov, Aug, and Sep
	Zarrindasht	Jan, Sep, Oct, Nov, Dec, and Feb
	Stahban	Jan, Feb, Apr, Aug, Sep, Oct, Nov, Dec, and May
	Shiraz	Jan, Sep, Oct, Nov, Dec, Feb, and Aug
	Sepidan	Jan, Oct, Nov, and Dec
	Pasargad	Sep, Oct, Nov, Dec, Jan, Feb, May, Jul, and Aug
	Marvdasht	Jan, Oct, Nov, Dec, Feb, Aug, and Sep
	Lar	Jan, Oct, Nov, Dec, and Feb
	Khonj	Jan, Oct, Nov, and Dec
	Kharame	Jan, Oct, Nov, Dec, Aug, and Sep
	Kazeroon	Jan, Oct, Nov, Dec, and Feb
	Jahrom	Jan, Oct, Nov, and Dec
	Ghirkarzin	Jan, Oct, Nov, Dec, Mar, May, Jun, Jul, Apr, Aug, and Sep
	Fasa	Jan, Oct, Nov, and Dec
	Farashband	Jan, Oct, Nov, and Dec
	Eghlid	Jan, Oct, Nov, Dec, Jun, Aug, and Sep
	Darab	Oct
	Bavanat	Jan, Oct, Nov, Dec, and Sep
	Abade	Jan, Oct, Nov, Dec, Feb, Aug, and Sep

4. Discussion

Based on the results of the current study, there were CL outbreaks regarding four different endemic values of CL resulted in setting four different alarm systems in different months of the year in Fars province, Iran. Based on the dedicated budget, policymakers and health managers could choose from these four alarms. For example, there were 20 cities as potential outbreaks regarding the past five year mean score, 19 cities regarding the past five year median score, 15 cities regarding the past five year median + IQR, and 7 cities regarding the past five year mean + 2SD as four distinctive alarm systems. Consequently, more budgets, staff, and health services are needed to control epidemics in the first alarm system, because 20 out of the 25 cities were detected as outbreaks and alarms should be set for all these areas in need of more facilities and money. However, the fewest budgets are called for the fourth alarm system regarding the fewest cities in the site (just 7 out of the 25 cities). What is noteworthy about all these alarm systems is that policymakers know the exact months of outbreaks in all four alarm systems. This could lower the dedicated budgets in the mentioned cities in the area. Moreover, six cities were detected to be common in outbreaks in all four scenarios. Abade, Eghlid, Marvdasht, Kharame, Stahban, and Fasa were at the highest risk of emerging epidemics of CL in 2016. Therefore, they must gain more attention and consideration, especially in January, August, September, October, and December. Since it was the first study done on setting Early Warning Systems on CL, especially in Iran, few studies were found with which the similarities and differences of the study results could be compared.

A factor that deserves further attention in setting Early Warning Systems is to understand the role of space. It was shown that developing Early Warning Systems for CL was a useful tool in estimating the large burden of disease in Costa Rica, ignoring space feature of CL. In that study, time-series models were used ending in a highly prediction accuracy from 50% to over 80%. However, in the present study, the space feature (the geographical trait) of CL was considered, which ended in a more trustworthy and complete Early Warning Systems[1,15]. Any phenomenon like CL is called a large-scale phenomenon since it undertakes rapid changes from instability in temperature to vast land changes and biological differences, all resulting in more trustworthy predictions[16,17]. One other consideration is that non-linear dynamics are common in nature, but are vastly considered by linear approximations[18,19]. With 25 different time-series models, 25 linear and non-linear trends were observed and regarded in the present study. Seasonality changes were controlled, as well.

As the endemic value got larger, fewer cities were found to be epidemic. Totally, six epidemic cities were common in all four maps regarding four different endemic values. Abade, Eghlid, Marvdasht, Kharame, Stahban, and Fasa were detected to be highly at risk of being infected with CL. Thus, more staff, budgets, and health products are required for these needy areas, resulting in curbing the incidence rate of CL and promoting individuals' public health in the whole site.

This study had some limitations that could affect the results. The surveillance system of CL in Iran is a passive system and too many patients with small lesions or lesions in masked parts of their bodies do not refer to health centers or surveillance systems. Therefore, the incidence rate of CL might still be underestimated. This could affect prediction of the disease load and also the required health services. Moreover, genetic factors as well as sero-epidemiological features of agents and vectors should be regarded to forecast CL, which would result in more trustworthy Early Warning Systems.

Fars province is an endemic site for leishmaniasis and, consequently, any effort on forecasting and controlling the disease can be of particular value. Future studies are suggested to regard more related factors like the number of rainy days, temperature, and humidity in addition to genetic factors to reach more reliable results in the area.

Early Warning Systems are helpful tools for neglected tropical and semi-tropical infections like malaria and leishmaniasis. ArcGIS is a powerful application in space epidemiology where a phenomenon is a space dependent variable. Early Warning Systems, using an earth-based analysis as well as a time-series analysis, can be a very powerful tool to predict an outbreak in future. Leishmaniasis is a time- and space-related variable whose incidence changes based on geographical as well as time changes. Available forecasting models have good capability to predict an outcome in future. Time-series models are very potent tools to accurately forecast a time related trait, particularly up to one year. Also, the predictability of time-series models depends on the validity and the count of in hand data as well as other available covariates, such as temporal-space and genetic ones. Forecasts can be useful in public health planning for the affected population, allowing estimation of an approximate number of vaccine shots, hospital beds, and vector control measures. Early Warning Systems incorporated with spatial spread of the infection dynamically consider the geographical pattern of the disease, leading to much better results for health managers and public health policymakers, so that they can focus on more congested parts and dedicate more services to more deserved areas. Since there is no unique way to develop Early Warning Systems for a given disease, there should be a general procedure to set it and make an alarm for health policymakers. The present research developed four main components for a vector-borne disease: (i) to define endemic values based on which we could verify if there was an outbreak, (ii) to set different time-series models to forecast the disease in future, (iii) to compare the forecasts with endemic values and decide on outbreak occurrence regarding both time and space, and (iv) to set an alarm to health managers. In this work, the main aims of Early Warning Systems were partially satisfied detecting different epidemic parts in the related time of the epidemic.

It is severely recommended to consider more related factors, such as the number of rainy days, temperature, and humidity, in addition to genetic factors in doing permutation scan statistics modeling introduced by Martin Culldorf to detect and forecast the spatiotemporal outbreaks in the area and then compare the results of the two methodologies as a validation process.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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