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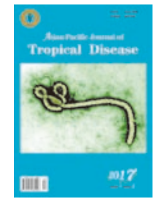

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Effect of temperature, rainfall and relative density of rodent reservoir hosts on zoonotic cutaneous leishmaniasis incidence in Central Tunisia

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ABSTRACT

Objective: To study the effect of climate variability and rodent density on the incidence of zoonotic cutaneous leishmaniasis (ZCL) in humans.
Methods: We collected monthly ZCL human cases in primary health care facilities, in schools and in the community. We collected monthly climate parameters such as temperature, humidity, rainfall, wind direction and wind speed, and rodent density. We investigated the relationship between ZCL incidence and climate and environmental variables by univariate and different multivariable analysis (multiple linear regression, negative binomial regression and autoregressive integrated moving average).
Results: The ZCL number peaked in October and November. In univariate analysis, positive associations were found for the maximum, mean and minimum temperatures lagged for three and six months, with higher correlation coefficient for the mean temperature lagged for six months (r = 0.837, P < 0.01). All multivariate analyses showed positive association between monthly ZCL incidence and the six months moving average temperature with higher correlation coefficients and very small significant level, whereas negative association was observed for the cumulative rainfall of the last year.
Conclusions: This work showed a significant association between ZCL incidence and climate variables suggesting that ecological early warning system could be applied for ZCL.

1. Introduction

Human health consequences of climate change are diverse and wide-ranging, resulting also in severe outbreaks of vector-borne infectious diseases and their likely geographic expansion, which pose a serious threat to vulnerable populations[1,2]. The pathways between climate change and the health outcomes are often complex and indirect. Indirect health impacts of changes in ecosystems or species consist on mediate zoonotic or vector-borne infectious diseases such as malaria, dengue fever, Hanta viruses, leishmaniasis, Lyme disease, schistosomiasis, *Henipahvirus*, etc. Climate changes including rainfall patterns, increase in temperature and humidity levels and also extreme events such as heatwaves, storms, cyclones, fires and floods constitute favorable conditions for the development and change in the distribution of mosquitoes and some other vectors leading to new disease patterns mainly in tropical and subtropical regionsin Africa[3]. Temperature affects insect's reproduction rate, biting behaviour and survival. Moreover, warmer temperatures tend to shorten the incubation period of pathogens inside vectors[1].

The world's most vulnerable populations, including children, pregnant women, elderly people, nomads, poor rural populations, refugees and people living in post-conflict settings are the most threatened by the already-high impact of changing climatic conditions on vector-borne diseases[4].

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The study protocol was performed according to the Helsinki declaration and approved by Pasteur Institute of Tunis Ethic Committee. Informed oral consent was obtained from adults and from parents for children.

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Tunisia is one of the identified nations of regional climate change hotspots[5]. As arid and semi-arid regions are among the most sensitive ecosystems to climate change[6,7], the poor rural population of Sidi Bouzid is the most threatened group by climate change impact including vector-borne diseases.

The transmission cycle of zoonotic cutaneous leishmaniasis (ZCL) is complex resulting from interactions between the *Leishmania major*, *Psammomys obesus* and *Meriones shawi* rodent reservoirs, accidental human hosts, and *Phlebetomus papatasi* and fly vectors. Favorable climate and environmental conditions influence all these implicated actors in the cycle and increase the risk of transmission[8,9].

ZCL caused by *Leishmania major* is the most common form of leishmaniasis in Tunisia. It is emerging and endemic in the centre and south of Tunisia since 1982–1983, and there is a periodicity of outbreaks of each 5–8 year intervals[10-14]. The emergence of ZCL coincides with the extension of land farming and water forage and exploitation in this area since the 1970s and the settlement of human population around irrigated fields[15] at the edges of the salt pan “Garaat Njila”. Previous studies showed high endemicity in districts which are close to this salt pan with agricultural activities as mainly occupation such as Hichria, Bir Bader and Zefzef[16]. The most common halolphytic plant in the salt pan “Garaat Njila” is chenopods which constitute the food of rodent reservoirs. Higher rainfall levels would increase the density of chenopods and consequently the reservoir density increases and affect ZCL transmission.

Currently, the biomedical model failed to control the spread of the diseases and to prevent epidemics. The used drug (meglumine antimoniate, glucantime) in the endemic areas is not always available, is expensive, and is not effective against the scar[17]. Vaccine prevention of leishmaniasis is not possible because there is no available vaccine to use.

Thus, the prevention of the disease is highly important mainly for the prediction of the epidemic and the implementation of control measure. Prediction needs the application of statistical models to understand the extent to which climate variability and climate change are affecting vector-borne infectious diseases burden, particularly modeling exposure-response relationships and the development of early warning systems (EWS) to develop useful models, which can be integrated by decision-makers in managing health risks[18].

The objective of this study was to investigate the relationship between climate and environmental factors and ZCL transmission on monthly observation in order to study the possibilities of EWS implementation based on climatic and environmental conditions, so as to predict epidemics well in advance and then implement control measures to limit the magnitude and the spread of the epidemics.

2. Materials and methods

2.1. Study area

The study was carried in Sidi Bouzid, Central Tunisia in three districts (Hichria, Bir Bader and Zefzef) (Figure 1), which are located at the edge of a sebkha or salt pan, Garaat Njila (35°46' N, 9°36' E, altitude 280 m), which is covered by a steppe of succulent halophilic vegetation composed predominantly of Chenopodiaceae of the genera *Salsola*, *Suaeda*and *Arthrocnemum* and occasional *Atriplex* sp.

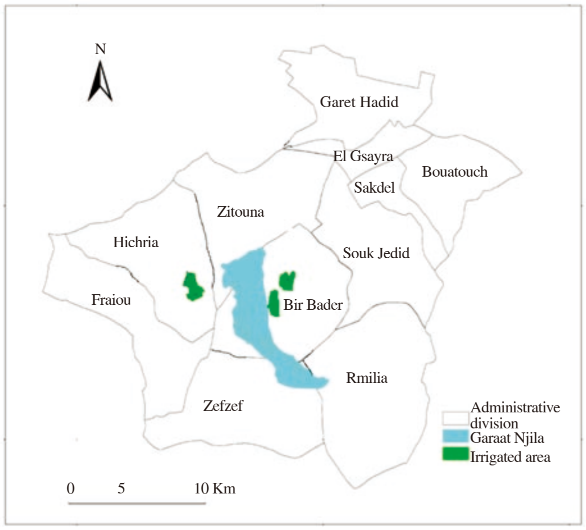

Figure 1. Location of the study areas (BirBadr, Hichria and Zefzef) in Sidi Bouzid, Central Tunisia.

2.2. Epidemiological data

We carried out a prospective cohort study for the whole population of these areas from July 2009 to June 2014 to detect new ZCL cases. ZCL notifications were obtained from an active system of epidemiologic surveillance, which was implemented in the three endemic districts since July 2009. This surveillance was based on the notification of all new cases in people who came to primary health care facilities seeking for treatment, and the active research of other cases among their neighbors and families by the nursing staff. All schools in this area have been asked to seek for and notify all ZCL cases among students. Moreover, the members of the research team performed a community-based active ZCL surveillance. Physicians and nurses from the health care facilities ascertained the diagnosis of cases notified in schools based on clinical inspection of the lesion or the scar. Parasitologic diagnosis of ZCL lesions was carried out only for a group of patients using direct examination, skin culture, PCR TaqMan and PCR high-resolution melting. We decided not to confirm the disease by laboratory exam because of the good knowledge of the disease by the medical staff and the population in this region and the high sensitivity and specificity of clinical diagnosis. The number of ZCL cases was reported on a standardized form. Then, the counting monthly incidence according to the date of the lesion onset was registered for the period of July 2009 to June 2014.

2.3. Environmental data

Climatic parameters were obtained from a weather forecasting station which was implemented in the study area, close by Garaat Njila, the focus of rodent reservoirs of ZCL. We collected monthly minimum (Tn), maximum (Tx) and mean temperature (Tm) in celsius degree, relative humidity (%), monthly cumulative rainfall quantity (mm), wind direction and wind speed. For temperatures (Tx, Tn and Tm), we calculated the moving average for each parameter on three (M-3), six (M-6) and nine (M-9) months ago and one (Y-1), two (Y-2), three (Y-3), four (Y-4) and five (Y-5) years ago. Cumulative rainfall quantity was also calculated for the same periods. Monthly rodent density was estimated from the count of active burrows on three consecutive days.

2.4. Rodent density

The density of rodents in the habitat represented by Garaat Njila (sebkha) was estimated monthly using a defined protocol. Indeed, we randomly selected three plots of one hectare surface area spread over the different edges of the sebkha. Each plot was divided into 10 sectors, and within each sector, we counted active burrows for each month and each parcel separately as follows: the first day we counted the number of open rodent burrows and we closed them; the second day we counted the number of re-opened burrows and we closed them again; on the third day, we just counted the number of re-opened burrows. The monthly density of rodents in three parcels was calculated through this equation:

$$\text{Rodent density} = \frac{\text{Number of burrows reopened at the 3rd day}}{\text{Number of burrows opened the first day}} \times 100$$

The monthly average density was the average of rodent densities in the three plots. This variable was calculated monthly and included in the data. We calculated also for each month, the density moving average for three, six and nine months ago.

We configured a monthly ecologic data. The dependent variable was the monthly incidence of ZCL and minimum, maximum and mean temperatures, relative humidity, rainfall and the average rodent density were the explanatory variables.

2.5. Statistical analyses

Seasonality of ZCL incidence and climatic variables was assessed by box plot representation. The relationship between ZCL occurrence and climate and environmental variables was investigated by different methods. First, we drew graphics for the dependent variable with all explanatory ones to explore possible fitness between ZCL number per month and climatic parameters, we also checked for graphic correlation between rainfall and rodent density. Then, we conducted a bivariate correlation analysis using the Spearman test between the dependent variable, monthly number of ZCL, and all climatic and environmental parameters.

We used three methods of multivariable analysis in order to identify strong and steady relationships between ZCL incidence and one or some of the climatic variables so that we could further use to study possibilities to implement EWS to predict ZCL epidemics.

Multivariate analysis was treated by multiple linear regressions using the incidence rate as dependent variable, as well as all the explanatory variables was quantitative and continuous. Backward stepwise elimination was used to generate the parsimonious model. We used R^2, also known as coefficient of determination, and the Durbin-Waston test to evaluate the model fit, the most appropriate linear model that fit well with observed data expected to have higher R^2 and a Durbin-Waston test value close to one.

The negative binomial regression with log link in generalized linear models was used instead of the Poisson regression, since the number of ZCL cases had a Poisson distribution, but the application condition of Poisson regression was not satisfied because the esperance of the number of ZCL cases was not equal to its variance. All significant independent parameters and those with a *P* value less than 0.20 were incorporated in the initial model, then many iterations were performed and compared through likelihood ratio until the final model with all statistically significant regression coefficients (at the 5% level) for each independent variable .

Finally, monthly ZCL number was estimated using an optimal form of an autoregressive integrated moving average (ARIMA) model with square root transfer function. The ARIMA transfer function models produced the closest fit[19]. The log transfer function was not possible because there were many months with zero ZCL cases. Cross-correlation method was used to select significant independent parameters and those with a *P* value less than 0.20. All possible combinations of these parameters were incorporated in ARIMA models using square transfer function for the dependent variable and then evaluated for the quality of fit. The closest fit ARIMA models were expected to exhibit a low normalized Bayesian criterion (BIC), a low mean absolute error (MAE), a large coefficient of determination (R^2) and statistically significant regression coefficients for each climatic parameter and ARIMA components [constant, autoregression (AR), moving average (MA)]. The quality of fit was further confirmed through autocorrelation and partial correlation functions analyses of model residuals.

The ARIMA model plots was used to predict the occurrence of epidemics by estimating the expected number of cases for each month from the observed data.

All statistical analyses and model developments were conducted using SPSS 19.0 at the two-tailed significance level of $P < 0.05$ (or the confidence level of 95%).

3. Results

From July 2009 to June 2014, a total of 859 (51.1% male, 48.9% female) new ZCL cases were registered in the three districts, with 393 (46%) cases between July 2013 and June 2014, only 80 cases for the season 2012–2013, 122 cases for the period 2011–2012, 206 ZCL cases in 2010–2011 and only 58 human ZCL cases between July 2009 and June 2010. The median age was 11 years (inter quartile range: 7–28), ranging from 2 months to 87 years and most of the patients were assigned to the 0–9 and 10–19 years age groups with approximately 40% and 30% of the total recorded ZCL cases respectively for each group. The analysis of the occurrence of cases over time showed that the number of ZCL cases started to increase from September. The ZCL number peaked in October, with an average number of ZCL of 50 and a total of 249 cases over the period, and November which cumulated 112 cases of ZCL with an average of 46. The monthly Tn and Tx reached their maximum in July, and high quantity of rainfall was observed during the warm season with a peak in September (Figure 2).

The peaks in the number of human cases of ZCL coincided exactly with those of the six months moving average of the mean temperature [Tm (M-6)], and with the ones of the cumulative rainfall of the previous three months [rainfall (M-3)], (Figures 3 and 4).

The emergence of a large number of human cases of ZCL was often preceded by a relatively high and sustained average density

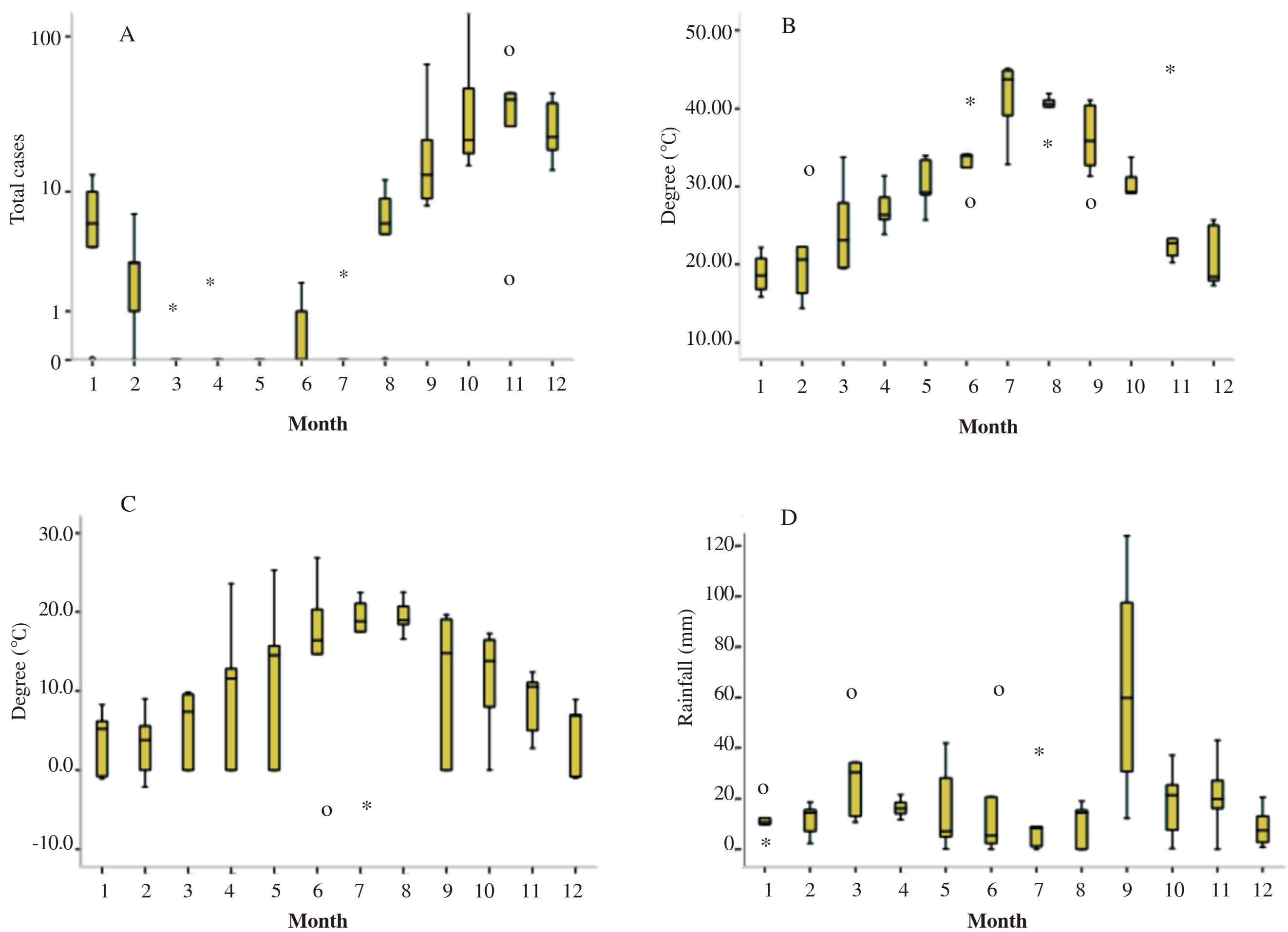

Figure 2. Box plot of the seasonal pattern of ZCL incidence (A), monthly average Tx (B), monthly average Tn (C), and monthly cumulative rainfall (D).

of rodents (Figure 5). The average density of rodents in the three parcels was dependent on cumulative rainfall quantity a year earlier [rainfall (Y-1)] (Figure 6).

Univariate analysis (Table 1) showed that there was a negative correlation between the incidence of ZCL and the average density of rodents and the average temperature during the same month [Tm (M0)]. Tn (M-3), Tn (M-6), Tx (M-3), Tx (M-6) Tm (M-3) and Tm (M-6) were highly correlated to the monthly number of human ZCL cases. We didn't find any significant association between ZCL cases and both wind direction and wind speed.

The multiple linear regression showed a positive association of the monthly incidence rate of ZCL with the Tm (M0) and the Tm (M-6), and a negative association with the Tx (M-3) and rainfall (Y-1). Tm (M-6) had the most important coefficient and a very small significant level *P*. The regression parameters were: R^2 = 0.720, Durbin-Waston = 1.118 and the multiple linear regression equation was:

ZCL incidence = 0.831 Tm (M0) + 3.42 Tm (M-6) – 1.034 Tx (M-3) – 0.228 rainfall (Y-1) – 489.33

The negative binomial regression (Table 2) showed that the increase of Tm (M-6) and rainfall (M-3) increased the monthly ZCL number and the increase of rainfall (Y-1) decreased ZCL incidence.

Table 2

Correlations between monthly ZCL cases and climate parameters, results from negative binomial regression.

Parameter	β	Exp β	95% confidence interval for Exp β	*P*
Rainfall (M-3)	0.280	1.028	1.003–1.053	0.025
Tm (M- 6)	0.403	1.497	1.367–1.639	0.000
Rainfall (Y-1)	-0.088	0.916	0.872–0.962	0.001
Constant	-5.291	-	-	0.000

Table 1

Univariate correlations between monthly ZCL incidence and seasonal climate variables 3 (M-3), 6 (M-6), 9 (M-9) months before, or during the same month (M0), and one year (Y-1), two years (Y-2), three years (Y-3), four years (Y-4) and five years (Y-5) before.

Variables	M0		M-3		M-6		M-9		Y-1		Y-2		Y-3		Y-4		Y-5	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
ARD	-0.362	0.004	0.133	NS	0.155	NS	-0.148	NS	-	NS	-	NS	-	NS	-	NS	-	NS
Tx	-0.216	0.097	0.583	< 0.000	0.705	< 0.000	0.298	0.210	-	NS	-	NS	-	NS	-0.187	0.152	-0.176	0.179
Tn	-0.187	0.153	0.636	< 0.000	0.826	< 0.000	0.222	0.088	-	NS	-	NS	-	NS	-	NS	-0.172	0.190
Tm	-0.292	0.023	0.579	< 0.000	0.837	< 0.000	0.142	NS	-	NS	-	NS	-	NS	-	NS	-	NS
Rainfall	0.289	0.148	0.219	0.093	0.041	NS	-0.780	NS	-0.168	0.20	-	NS	-	NS	-	NS	-	NS
RH (day)	0.152	NS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
RH (night)	0.174	0.184	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

ARD: Average rodent density; RH: Relative humidity; r: Spearman coefficient; NS: Not significant.

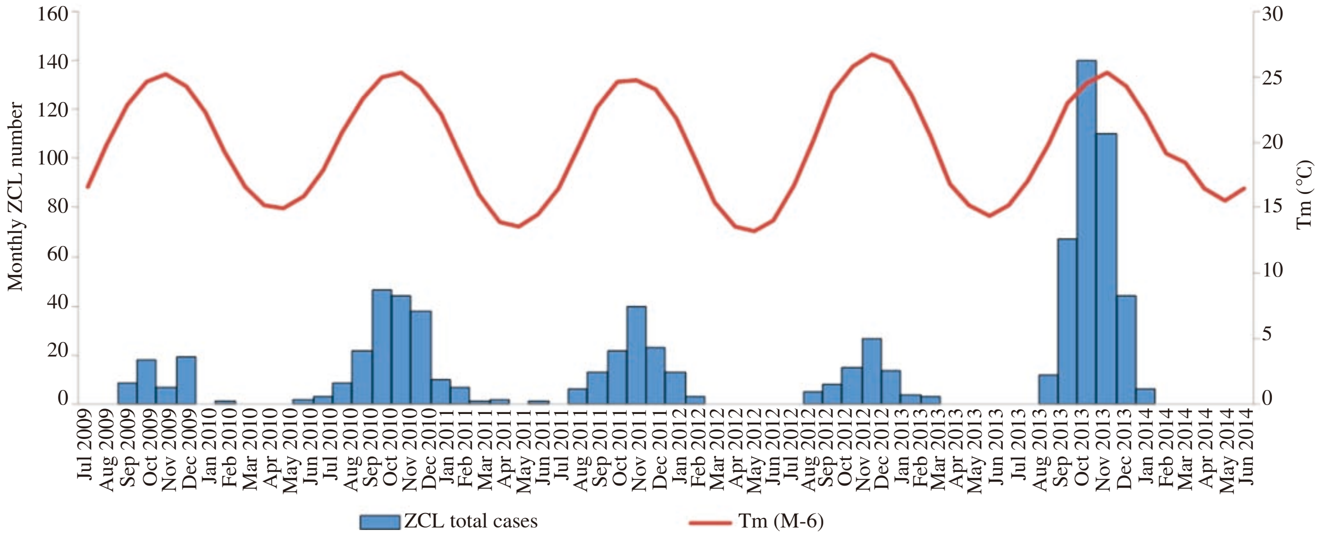

Figure 3. Reported cases of ZCL per month and the six months moving average of Tm, July 2009–June 2014.

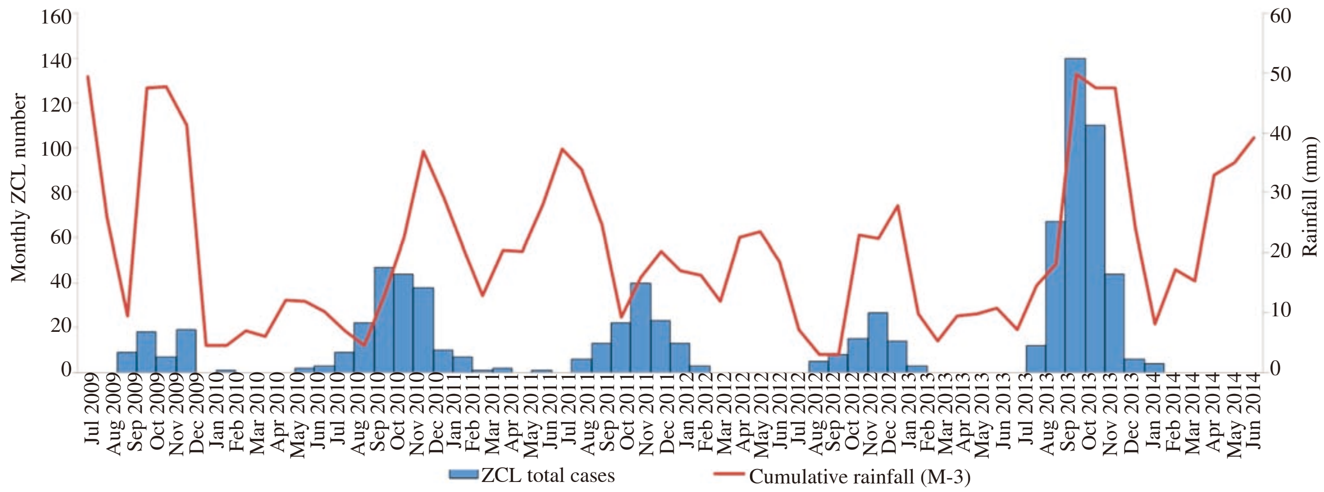

Figure 4. Monthly reported cases of ZCL and the cumulative rainfall of the three previous months, July 2009–June 2014.

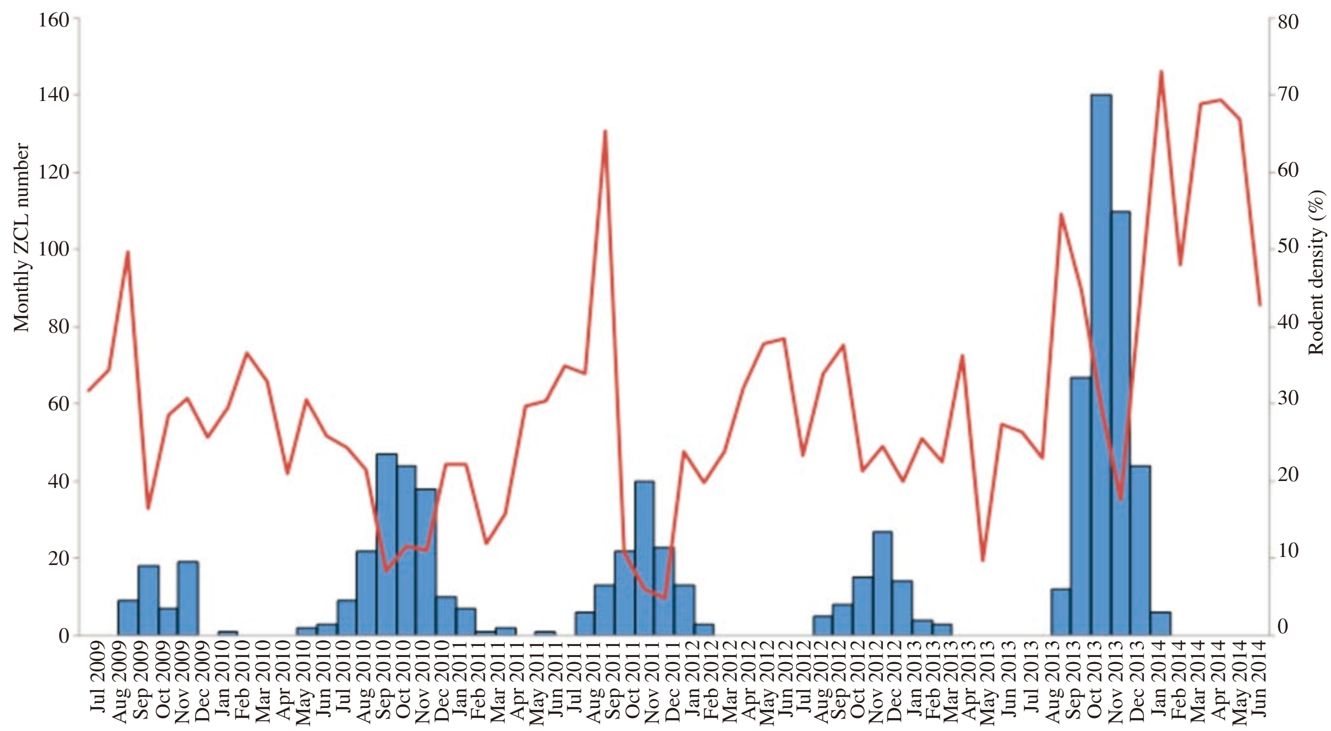

Figure 5. Reported cases of ZCL and the average of rodent density, July 2009–June 2014.

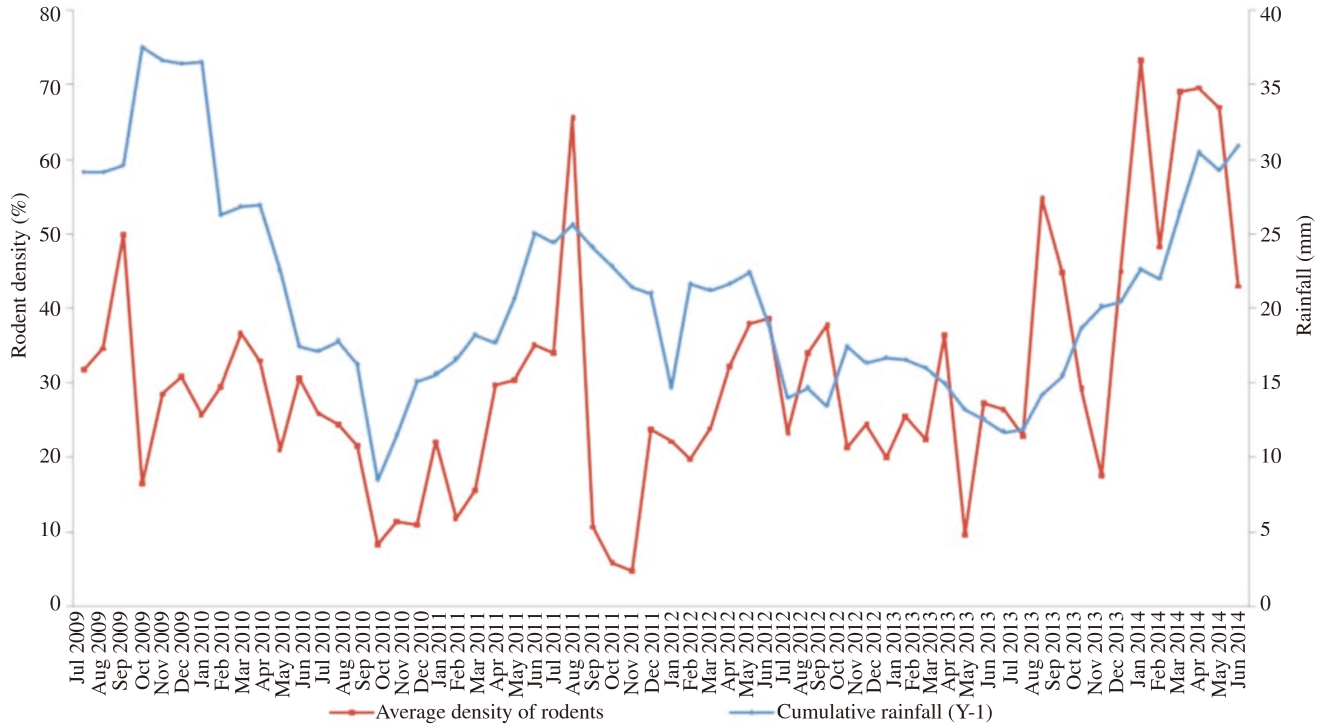

Figure 6. Average density of rodents and the cumulative rainfall during the last year, July 2009–June 2014.

In time series analysis, predictors are fitted with an ARIMA, AR (1) model using square root transfer function (168 total models were realized and compared according to their normalized BIC, MAE, R^2, all significant regression coefficients and residuals). The final model satisfied all performance expectations (lower normalized BIC, lower MAE, larger R^2, significant coefficients, and the remaining residuals exhibited no significant trend or autocorrelation (Figure 7).

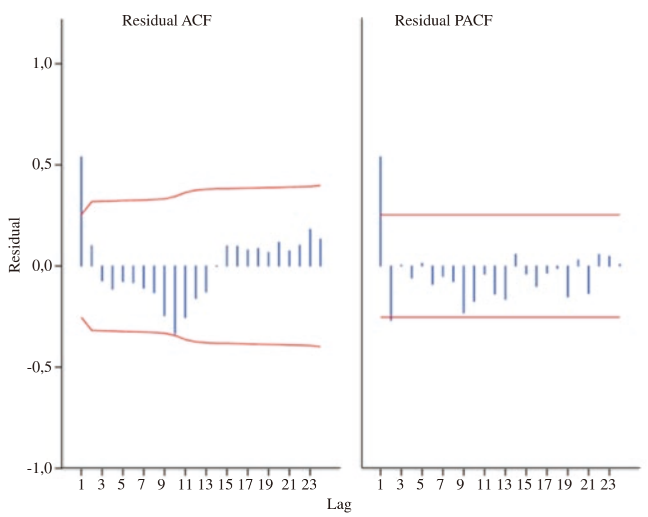

Figure 7. Residual autocorrelation and partial autocorrelation functions from the final ARIMA AR(1) model.
ACF: Autocorrelation function; PACF: Partial autocorrelation function.

The ARIMA AR(1) model showed a positive association between the monthly incidence of ZCL and the Tm (M0), rainfall (M0), rainfall (M-3) and Tm (M-6). The Tx (M0) and rainfall (Y-1) were negatively associated with the monthly incidence of ZCL (Table 3).

The 2013–2014 season corresponded to an epidemic year over the 5 years period, and the number of observed cases exceeded the upper limit of the confidence interval (Figure 8).

Table 3
Correlations between monthly ZCL cases and climate parameters, results from times-series analysis with ARIMA AR(1) model.

Parameters	Estimate	Standard error	*P*
Tm (M0)	0.102	0.046	0.030
Tx (M0)	-0.077	0.032	0.019
Rainfall (M0)	0.014	0.006	0.025
Rainfall (M-3)	0.076	0.070	0.000
Tm (M-6)	0.509	0.070	0.000
Rainfall (Y-1)	-0.123	0.049	0.014
Constant	-6.608	2.130	0.003
AR(1)	0.673	0.110	0.000

Model expectations: R^2 = 0.864; MAE = 5.26; Normalized BIC = 5.41.

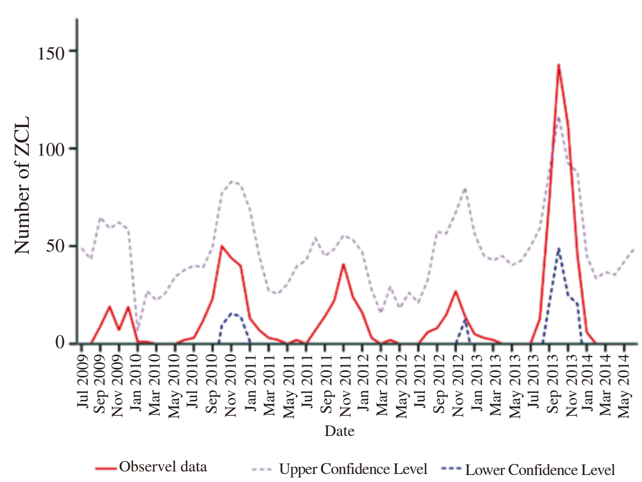

Figure 8. Estimation of expected values (UCL, LCL) and prediction of the epidemic season by the ARIMA model plots.

4. Discussion

ZCL is a vector-borne disease common in tropical and subtropical regions including North Africa. In Tunisia, ZCL is a major public health problem for the health care system, an epidemic emerged in some central areas first and expanded rapidly to the whole central and southern parts of the country since 1982[11-14,20]. ZCL is not a severe disease, but it leaves an indelible scar on the faces of patients, after the skin lesions which lead to significant social consequences such as stigmatization, mainly in girls and women.

In this study, we monitor simultaneously human new cases of ZCL, climate parameters and rodent density over a period of five years at a local scale. The aim was to investigate the relationship between monthly ZCL incidence and temperatures, precipitation and rodent density in order to assess the possibilities of the establishment of an early warning system based on one or some of these variables to detect epidemics seasons in advance and implement control measure with the local population.

Our data suggested that ZCL is still highly endemic in Central Tunisia areas and the 2013–2014 was an epidemic season over the five years-period. The influence of meteorological factors on ZCL transmission during 2009–2014 has been established at monthly time scales throughout different statistical analyses methods. Significant bivariate correlation between monthly ZCL number and local climate parameters were identified. Positive associations were found for the Tx, Tm and Tn lagged for three and six months, whereas negative associations were observed for the average rodent density and Tm during the same month. All multivariate analyses showed positive association between monthly ZCL incidence and the six months moving average temperature (Tm (M-6)) with high correlation coefficients and very small significant level, whereas negative association was observed for the cumulative rainfall of the last year [rainfall (Y-1)].

In this work, some limitations should be pointed out. ZCL reported number could be incomplete since some cases should be missed. However leishmaniasis occurs commonly in this area so that it is not necessary for all cases to be reported and this should not reduce the effectiveness of surveillance.

This work is interesting since it is the first study in Tunisia which used data from ZCL active surveillance system and climate variables monitored by private weather station that was implemented in the study area giving more precision for these parameters.

Simultaneous monitoring ZCL cases, meteorological parameters and environmental conditions in the study area gave us more real and precise data. These ecological data of sixty observations allowed us to investigate relationship between ZCL transmission and climate parameters using different statistical methods and found consistent results. Multivariate autoregressive models with square root transformation showed precision (high R^2) and skill (low MAE, low normalized BIC). As in previous studies[19], the ARIMA transfer models in times-series analysis produced the most appropriate fit in modeling transmission of infectious diseases for early warning system implementation. However, it needs time series sufficiently long for developing and evaluating forecasting models.

Our study suggested that the epidemic curve displays peak and inter-epidemic periodicity of 5 years as shown by Toumi *et al*.[10] on a long series observation. Key factors driving temporal dynamics of ZCL transmission in Tunisia are not well studied. Based on our time series analysis, climate parameters play a significant role in ZCL transmission. We showed for the first time, that the average temperature six months ago is the most important predictor for ZCL incidence. Toumi *et al.*[10] demonstrated the relation between humidity and rainfall lagged for 13–15 months and ZCL incidence in Sidi Bouzid, but the temperature was not associated to ZCL incidence. However, Toumi *et al*.[10] used different source of data and different area for the study. They used the number of ZCL cases from the routine passive detection and climate variables from the Tunisian National Institute of Metrology. Data were collected and analyzed for all the governorate of Sidi Bouzid. In our study, we used data from an active monitoring system that was implemented in a small area.

Although, it's well known that the ambient temperature determines insect's reproduction rate, biting behaviour and survival. Moreover, the incubation period of pathogens inside vectors tends to be shorter at warmer temperatures. Previous studies showed that temperature affects significantly the density and dynamics of *Phlebotomus papatasi*[21-24]. The work of Kassem *et al*.[25] in the Nile Delta revealed that sand fly densities were strongly correlated to temperature but not to relative humidity or wind velocity. However, the study of Bounoua *et al*.[26] in Algeria demonstrated that the establishment of new endemic foci in regions that were not previously endemic was related to sufficient increase in minimum temperatures. Cutaneous leishmaniasis in Brazil[27] has a marked seasonality and is linked with dry and warm conditions of the following season, which favor the vectors and fly development.

The increase of cumulative rainfall level for the previous three months increases the ZCL incidence but, the decrease of rainfall for the last year increases ZCL number. Higher rainfall quantities in the previous three months would increase the density of chenopods, a halophytic plant that constitute the main source of rodent's reservoirs feeding. Consequently the reservoir density increases, and affects the ZCL transmission. The negative association between rainfall lagged for 12 months and the incidence of the disease could be explained by indirect factors such as the exposition of the farmers and their family member's to the sand fly bites due to intensive and frequent irrigation after a dry season. Also, very high levels of rainfall during the previous 12 months would cause flooding which would reduce the density of chenopods and thus the population of rodents.

Similar findings was observed in Golestan Province in Iran[28] and in French Guiana[29] where ZCL incidences were negatively correlated with rainfall, and the number of rainydays and positively correlated with temperature. Gholamrezaei *et al*.[30], found that mean annual temperature and seasonal precipitation contribute to the potential distribution of main reservoir hosts of ZCL in Iran.

CL incidence rates in Jordan, Syria, Iraq and SaudiArabia[31] seem to have a positive relationship with precipitation and negative relationship with temperature. Though, no relationship was identified betweenthe disease incidence rates and the humidity.

As there is no vaccine against ZCL and the treatment is not effective for the scar, rapid case detection and treatment can't reduce the epidemic. Moreover, control measures against rodents and vectors are also not effective and very harmful to the environment[17]. Thus, predicting epidemics well in advance and control measures implementation within the population such as self protection from sandfly bites by reducing their exposure outside and inside habitation could reduce the impact of the epidemic mainly in most vulnerable people such as children and women.

Prediction of epidemics through early warning systems is a high research priority to improve the response of control programs of ZCL. The present study established that early warning systems based on climate parameters is a feasible application for ZCL. However, some questions need to be addressed when modeling ZCL transmission: first, a sustained surveillance and monitoring efforts of ZCL and climate and environmental factors is needed to provide time series sufficiently long for developing and evaluating forecasting models. A minimum of ten years period is needed to establish a time series data, so that model can be developed in 70% of the data and assessed and validate in the other 30%. Second, the appropriate functional form to introduce also the dependent and climate variables[32] and the appropriate approach for modeling seasonality[33] should be further investigated. Finally, models should be evaluated and compared for predictability with "out-of-fit" data and not simply quality of fit[34-36] and for the robustness of the relationship with covariates in the selected model[37].

Conflict of interest statement

We declare that we have no conflict of interest.

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References

[1] McMichael AJ, Lindgren E. Climate change: present and future risks to health, and necessary responses. *J Intern Med* 2011; **270**: 401-13.

[2] Dhimal M, Ahrens B, Kuch U. Climate change and spatiotemporal distributions of vector-borne diseases in Nepal-a systematic synthesis of literature. *PLoS One* 2015; **10**(6): e0129869.

[3] Githeko AK, Lindsay SW, Confalonieri UE, Patz JA. Climate change and vector-borne diseases: a regional analysis. *Bull World Health Organ* 2000; **78**(9): 1136-47.

[4] Kelly-Hope L, Thomson MC. Climate and infectious diseases. In: Thomson MC, Garcia-Herrera R, Beniston M, editors. *Seasonal forecasts, climate change and human health*. New York: Springer; 2008, p. 31.

[5] Diffenbaugh NS, Giorgi F, Raymond L, Bi X. Indicators of 21st century socioclimatic exposure. *Proc Natl Acad Sci U S A* 2007; **104**(51): 20195-8.

[6] Maestre FT, Salguero-Gomez R, Quero JL. It is getting hotter in here: determining and projecting the impacts of global environmental change on drylands. *Philos Trans R Soc Lond B Biol Sci* 2012; **367**: 3062-75.

[7] Vicente-Serrano SM, Zouber A, Lasanta T, Pueyo Y. Dryness is accelerating degradation of vulnerable shrublands in semiarid Mediterranean environments. *Ecol Monogr* 2012; **82**: 407-28.

[8] Ready PD. Leishmaniasis emergence and climate change. *Rev Sci Tech* 2008; **27**: 399-412.

[9] Cardenas R, Sandoval CM, Rodríguez-Morales AJ, Franco-Paredes C. Impact of climate variability in the occurrence of leishmaniasis in northeastern Colombia. *Am J Trop Med Hyg* 2006; **75**: 273-7.

[10] Toumi A, Chlif S, Bettaieb J, Ben Alaya N, Boukthir A, Ahmadi ZE, et al. Temporal dynamics and impact of climate factors on the incidence of zoonotic cutaneous leishmaniasis in Central Tunisia. *PLoS Negl Trop Dis* 2012; **6**: e1633.

[11] Ben Ismail R, Gradoni L, Gramiccia M, Bettini S, Ben Rachid MS, Garraoui A. Epidemic cutaneous leishmaniasis in Tunisia: biochemical characterization of parasites. *Trans R Soc Trop Med Hyg* 1986; **80**: 669-70.

[12] Ben-Ismail R, Ben Rachid MS, Gradoni L, Gramiccia M, Helal H, Bach-Hamba D. [Zoonotic cutaneous leishmaniasis in Tunisia: study of the disease reservoir in the Douara area]. *Ann Soc Belg Med Trop* 1987; **67**: 335-43. French.

[13] Ben Ismail R, Ben Rashid MS. Epidémiologie des leishmanioses en Tunisie. Maladies tropicales transmissibles Ed AUPELF-UREE John Libbey Eurotext Paris; 1989, p. 73-80.

[14] Salah AB, Kamarianakis Y, Chlif S, Alaya NB, Prastacos P. Zoonotic cutaneous leishmaniasis in central Tunisia: spatio temporal dynamics. *Int J Epidemiol* 2007; **36**: 991-1000.

[15] Abaab A. Agricultural modernization and regional development in Central Tunisia (as in Sidi Bouzid region). In: Jouve AM, ed. *The modernization of Mediterranean agriculture (in memory of Pierre Coulomb)*. Montpellier: CIHEAM; 1997, p. 249-54. French.

[16] Bellali H, Ben Alaya N., Ahmadi Z, Ennigrou S, Chahed MK. Eco-environmental, living conditions and farming issues linked to zoonotic cutaneous leishmaniasis transmission in Central Tunisia: a population based survey. *Int J Trop Med Public Health* 2015; **5**(1): 1-7.

[17] World Health Organization. Control of the leishmaniases. Report of a meeting of the WHO Expert Committee on the control of leishmaniases. Geneva: World Health Organization; 2010. [Online] Available from: http://apps.who.int/iris/bitstream/10665/44412/1/WHO_TRS_949_eng.pdf [Accessed on 2rd September, 2016].

[18] Ebi KL, Rocklöv J. Climate change and health modeling: horses for courses. *Glob Health Action* 2014; **7**: 24154.

[19] Chaves LF, Pascual M. Comparing models for early warning systems of neglected tropical diseases. *PLoS Negl Trop Dis* 2007; **1**: e33.

[20] Bettaieb J, Toumi A, Chlif S, Chelghaf B, Boukthir A, Gharbi A, et al. Prevalence and determinants of leishmania major infection in emerging and old foci in Tunisia. *Parasit Vectors* 2014; **7**: 386-93.

[21] Benkova I, Volf P. Effect of temperature on metabolism of *Phlebotomus papatasi* (Diptera: Psychodidae). *J Med Entomol* 2006; **44**: 150-4.

[22] Kasap OE, Alten B. Comparative demography of the sand fly *Phlebotomus papatasi* (Diptera: Psychodidae) at constant temperatures. *J Vector Ecol* 2006; **31**: 378-85.

[23] Almeida PS, Andrade AJ, Sciamarelli A, Raizer J, Menegatti JA, Hermes SC, et al. Geographic distribution of phlebotomine sandfly species (Diptera: Psychodidae) in Central-West Brazil. *Mem Inst Oswaldo Cruz* 2015; **110**(4): 551-9.

[24] Sangiorgi B, Miranda DN, Oliveira DF, Santos EP, Gomes FR, Santos EO, et al. Natural breeding places for phlebotomine sand flies (Diptera: Psychodidae) in a Semiarid Region of Bahia State, Brazil. *J Trop Med* 2012; **2012**: 124068.

[25] Kassem HA, El-Sayed YA, Baz MM, Kenawy MA, El Sawaf BM. Climatic factors influencing the abundance of *Phlebotomus papatasi* (Scopoli) (Diptera: Psychodidae) in the Nile Delta. *J Egypt Soc Parasitol* 2009; **39**: 305-16.

[26] Bounoua L, Kahime K, Houti L, Blakey T, Ebi KL, Zhang P, et al. Linking climate to incidence of zoonotic cutaneous leishmaniasis (*L. major*) in Pre-Saharan North Africa. *Int J Environ Res Public Health* 2013; **10**: 3172-91.

[27] Ferreira de Souza RA, Andreoli RV, Toshie Kayano M, Lima Carvalho A. American cutaneous leishmaniasis cases in the metropolitan region of Manaus, Brazil: association with climate variables over time. *Geospatial Health* 2015; **10**: 314-21.

[28] Shirzadi MR, Mollalo A, Yaghoobi-Ershadi MR. Dynamic relations between incidence of zoonotic cutaneous leishmaniasis and climatic factors in Golestan Province, Iran. *J Arthropod Borne Dis* 2015; **9**(2): 148-60.

[29] Roger A, Nacher M, Hanf M, Drogoul AS, Adenis A, Basurko C, et al. Climate and leishmaniasis in French Guiana. *Am J Trop Med Hyg* 2013; **89**(3): 56-9.

[30] Gholamrezaei M, Mohebali M, Hanafi-Bojd AA, Sedaghat MM, Shirzadi MR. Ecological niche modeling of main reservoir hosts of zoonotic cutaneous leishmaniasis in Iran. *Acta Trop* 2016; **160**: 44-52.

[31] Jaber SM, Ibbini JH, Hijjawi NS, Amdar NM, Huwail MJ, Al-Aboud K. Exploring recent spatial patterns of cutaneous leishmaniasis and their associations with climate in some countries of the Middle East using geographical information systems. *Geospatial Health* 2013; **8**(1): 143-58.

[32] Cazelles B, Hales S. Infectious diseases, climate influences and nonstationarity. *PLoS Med* 2006; **3**: e328.

[33] Altizer S, Dobson A, Hosseini P, Hudson P, Pascual M, Rohani P. Seasonality and the dynamics of infectious diseases. *Ecol Lett* 2006; **9**: 467-84.

[34] Chaves LF, Pascual M. Climate cycles and forecasts of cutaneous leishmaniasis, a nonstationary vector-borne disease. *PLoS Med* 2006; **3**: e295.

[35] Levins R. Strategies of abstraction. *Biol Philos* 2006; **21**: 741-55.

[36] Selmane S. Dynamic relationship between climate factors and the incidence of cutaneous leishmaniasis in Biskra Province in Algeria. *Ann Saudi Med* 2015; **35**(6): 445-9.

[37] Levins R. The strategy of model building in population biology. *Am Sci* 1996; **54**: 421-31.