Türkiye Parazitoloji Dergisi, 33 (1): 8 - 14, 2009
Türkiye Parazitol Derg.

Determination of High Risk Regions of Cutaneous Leishmaniasis in Turkey Using Spatial Analysis

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SUMMARY: The aim of this study was to use geographical analysis to determine the distribution of cutaneous leishmaniasis among the provinces of Turkey, as well as detection of the presence of any regional clustering in Turkey using spatial analyses. Geographic information systems based spatial analyses were performed on cutaneous leishmaniasis cases recorded by the Turkish Ministry of Health during the period from 1988-2006. Spatial analyses, including local and global spatial autocorrelation methods and clustering analysis were performed on the cutaneous leishmaniasis cases (1996-2006), to detect any trend or cluster and any particular province. The spatial distribution of cutaneous leishmaniasis cases was nonrandom and found to be clustered significantly ($p<0.05$). There is a clear trend toward the southeast region. Regions with high concentration of cutaneous leishmaniasis are located in the southeast region ($p<0.05$). This study shows that cutaneous leishmaniasis is a serious public health concern in the southeast region of Turkey, and that region should have a priority in the implement of precautionary measures. It also shows that spatial analyses and statistics can contribute to the understanding of the epidemiology of diseases and in identification of high rate disease locations.

Key Words: Cutaneous Leishmaniasis, Epidemiology, Geographic Information Systems, Spatial Analysis

Türkiye'de Leishmaniasis İçin Riskli Bölgelerin Mekansal Analiz Yöntemleri Kullanılarak Belirlenmesi

ÖZET: Bu çalışmada coğrafik bilgi sistemleri ve mekansal analiz yöntemleri kullanılarak, Türkiye'de illere göre kutanöz leishmaniasisin dağılımının ve bölgesel bir kümelenmenin olup olmadığının belirlenmesi amaçlanmıştır. T.C Sağlık Bakanlığı'nın 1988-2006 yılları arasındaki kayıtlı kutanöz leishmaniasisin vakalarına ait veriler, coğrafi bilgi sistemlerinin bünyesinde bulunan mekansal analiz yöntemleri ile değerlendirildi. Bu verilerin 1996-2006 yıllarına ait olanları lokal ve global mekansal otokorelasyon yöntemleri uygulanarak, illerde kutanöz leishmaniasis vakalarında bir trend veya kümelenme olup-olmadığı analiz edildi. Kutanöz leishmaniasis vakalarının mekansal dağılımının tesadüfi olmadığı ve istatistiksel açıdan anlamlı olarak bir kümelenme gösterdiği mekansal analiz yöntemleriyle tespit edilmiştir ($p<0.05$). Mekansal analizler kullanılarak, kutanöz leishmaniasis vakalarında Türkiye'nin güneydoğusuna doğru bir trend belirlenmiş ve kutanöz leishmaniasis vakalarında yoğunlaşma görülen yerlerin güneydoğu bölgesinde yer aldığı saptanmıştır ($p<0.05$). Bu çalışma, kutanöz leishmaniasisin özellikle Türkiye'nin güneydoğusu için sıklık açısından önemli bir halk sağlığı sorunu olduğunu, dolayısıyla hastalığın önlenmesinde koruyucu önlemlerin alınması için öncelikli bölge olması gerektiğini göstermektedir. Bu çalışma aynı zamanda mekansal analiz ve istatistik yöntemlerinin hastalık hızının yüksek olduğu yerleri belirlemede olduğu kadar, hastalıkların epidemiyolojisini anlamada katkıda bulunabileceğini de göstermektedir.

Anahtar Sözcükler: Kutanöz leishmaniasis, Epidemiyoloji, Coğrafi Bilgi Sistemi, Mekansal Analiz

INTRODUCTION

Leishmaniasis is a group of zoonotic infections caused by protozoan parasites of the genus *Leishmania*. The number of leishmaniasis is increasing globally at an alarming rate irrespective of the region and the leishmaniasis is amongst the top emergent diseases in spite of control measures. Leishmaniasis have expanded beyond their natural ecotypes due to the ecological change caused by human and this in turn affects the levels of his exposure to the vectors (1). It is estimated that new cases of 2 millions occur every year in the world, of which 1.5 million cases are cutaneous leishmaniasis (CL). An estimated 12 million people are presently infected worldwide (2, 3).

Makale türü/Article type: **Araştırma / Original Research**
Geliş tarihi/Submission date: 08 Ocak/08 January 2008
Düzeltme tarihi/Revision date: 23 Şubat/23 February 2009
Kabul tarihi/Accepted date: 24 Mart/24 March 2009
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Public health management and disease control studies are important duties for health agencies, governments, and researchers to improve human health (4). Disease maps have been playing a key descriptive role in public health and epidemiology. These maps are useful tools for many purposes such as; identification of areas of the current geographical distribution of the incidences of diseases, and assisting in the formulation of hypotheses about disease etiology, and assessing potential needs for geographical variation in follow-up studies (5). With the development of information system technology over the last 30 years, geographic information systems (GIS) have begun to be used as a tool to visualize, manage, explore and analyze spatial data with spatial analysis methods that are included in GIS software's modules in public health and epidemiologic researches (6).

Turkey represents a crossroad between the Europe and Asia continents, and shows different ecological and climatic conditions, which are important in the epidemiology of leishmaniasis (7). Some of the countries where CL is endemic show similar anthropologic characteristics with Turkey, especially with Southeastern Anatolia Region (8).

CL is considered to show different distributions and clusters, because of the geographical, economical, environmental and cultural differences among the provinces of Turkey. Many of the researchers report different provinces as endemic looking only for the number of the CL cases. Although no study was performed on the CL using GIS and spatial analysis, many of the researchers reported different provinces as endemic based on the number of the CL cases. Therefore, we aimed to explore presence of any regional clustering of CL in Turkey using GIS and spatial analyses.

MATERIAL AND METHODS

Study Area: Turkey is both a European and Middle Eastern country, which is surrounded by Bulgaria at the northwest, Georgia at the northeast, Armenia and Iran at the east, Syria and Iraq at the south. There are seven major geographical regions in the country as follows: Marmara, Aegean, Mediterranean, Central Anatolian, Black Sea, Eastern and Southeastern Anatolian regions. It is generally known that Eastern and Southeastern Anatolian regions are less developed regions than the other ones socioeconomically. Also, there are a total of 81 provinces in these seven regions in the country.

CL databases: In Turkey, Ministry of Health requires mandatory reporting of certain communicable diseases including the CL in the health facilities. All data regarding the total numbers of diagnosed CL cases recorded in Turkey between the years 1988-2006 were obtained from the Ministry of Health of Turkey (9). The data regarding the distribution of the CL cases to provinces between the years 1996-2006 were also obtained from the Ministry of Health of Turkey, since there were no available provincial records for the years of 1988-1995. Thus, the data for the years 1996 to 2006 were used for spatial analyses. Population by census year, annual intercensal rate of increase, and mid-year population forecast data of the provinces were obtained from Turkish Statistical Institute (10).

Statistical Methods and Calculations: Different software's were used for visualization and spatial analysis of the disease data in the study. These are; Arc GIS 9.3 developed by ESRI, GeoDa 0.9.5-I developed by Luc Anselin through the Center for Spatially Integrated Social Science at the University of Illinois (11); CrimeStat 3.1 developed by Ned Levine, with support form the National Institute of Justice (12); and SaTScan 7.0.3 developed by Martin Kulldorff with support from the National Cancer Institute (NCI) (13, 14).

Spatial Analyses: Province unit is a common level for social, economic, demographic, and administrative data collection by the agencies in Turkey. Therefore, CL cases were examined by aggregating to the province level with spatial analyses in the study. However, province units have important limitations; provinces are administrative units, and cover large areas with different heterogeneous populations, and they might not match the ecological scale. Meanwhile it is taught that aggregating the incidence rates for the entire eleven years provides the advantage of stability in the province-level CL rates, and it summarizes the phenomenon.

Population density was used as a standardization factor in the study. The morbidity rate is the number of CL cases based on Ministry records in a province during one year divided by the total number of inhabitants residing in that province in the middle of that year. Then, average raw morbidity rates were calculated for the 1996-2006 period according to the provinces.

Excess risk rate, a commonly used notion in rate analyses, which reflects the concept of a standardized morbidity rate or, the ratio of the observed morbidity rate to a national standard was used in the study. The excess risk is the ratio of the observed rate to the average rate computed for all the CL data. This average is not the average of the province rates, but calculated as the ratio of the total sum of all cases over the total sum of all populations at risk.

Since the incidence rates were aggregated into the areal units of provinces, an important aspect is to derive spatial weight matrix (W) for explorative spatial analyses. W is the fundamental tool used to model the spatial proximity and interdependence among areal units. Determination of the proper W matrix is a difficult and controversial topic in spatial analyses.

In this study, three different methods were used to obtain W matrices. The first and second matrices were calculated based on the criterion of contiguity according to the centroid of nearest 6-12 neighbor provinces, and the third matrix was formed according to the criterion of inverse distance.

While working with aggregated data, if the population or the number of cases belong the provinces is relatively small and sparsely, rate estimates may not be precise. In order to overcome this problem of rate instability, various smoothing methods are usually employed (15, 16). The idea in smoothing is to borrow the information from other small areas for the estimation of the relative risk. In this study, Empirical Bayes (EB) smoothing was used and raw rates were replaced with their globally smoothed values calculated by EB tool in Arc GIS 9.3 which created as a script by National Cancer Institute of USA (15, 17). After rate smoothing was constructed, a spatial rate smoothing based on the notion of a spatial moving average was constructed for explorative spatial data analysis. The purpose of integrating spatial rate smoother method was to emphasize global variations and trends in the CL data by averaging rates under a moving window (15).

In order to explore spatial dependence, showing how the incidence rates are correlated in the country, Moran's I and Geary C values were calculated with three W matrices. Moran's I and Geary C uses the magnitude of incidence rates to identify and measure the strength of spatial patterns. Moran's I statistics for CL incidence rates is calculated based on the assumption of constant variance. This assumption is usually violated when incidence is varied in different populations. Therefore, Assuncao-Reis Empirical Bayes standardization was performed to Moran's I values to adjust for the violation of the assumption (11, 18). For both Moran's I and Geary C the statistical significance which how confident you can be that any pattern is not simply due to chance, can be calculated through either the normal approximation or by randomization experiments. The range of possible values of Moran's I is -1 to 1. Positive values indicate spatial clustering of similar values while negative values indicate a clustering of dissimilar values. The range of possible values of C is 0 to 2. A value of **c** close to 0 means the distribution of values clustered, conversely **a** value of C close to 2 means the distribution of values dispersed.

Moran's I and Geary's C methods indicate clustering of high or low values. Nevertheless, these methods cannot distinguish between these situations. Hence, General G statistics was used to understand clustering of high or low incident rates. General G statistics shows existence of either hot spots or cold spots in the region. A large value of G statistics bigger than expected G statistics means that high values are found together converse, a small value of G statistics means low values are found together.

These global spatial data analyses show clustering but they do not show where the clusters are. To investigate the spatial variation as well as the spatial associations, it is possible to calculate local versions of Moran's I, Geary's C, and the General G statistics for each province in the data. Local indicators produce a specific value for each province allowing the identification of where the clusters are. Local Moran's I (LISA) (19) and G_i* statistics of Getis and Ord (20) indices were used to explore where the diseases are clustered in the country. Firstly, local analyses based on the LISA statistics were visualized in the form of significance and cluster maps. Secondly, G statistics was used to detect local pockets of dependence that may not show up when using global spatial autocorrelation methods, suggested by Getis and Ord (20, 21).

Another method to test for the presence of CL infection clusters and to identify their location was spatial scan statistics which developed by Kulldorff et al. (13, 14). This method has several features that make it particularly suitable as a screening tool for evaluating potential disease clusters that have been described in detail elsewhere (13, 14, 22). This method takes into account the uneven spatial distribution of cases and population densities. It does not require a priori assumptions about the number, place, or size of locations that may be identified as clusters. It adjusts for multiple testing inherent in the search for multiple clusters; and it searches for either high or low incidence areas (23). The geographic distribution of the number of cases in each province was assumed to follow a Poisson distribution in the study. The most likely spatial cluster was determined by computing maximum likelihood ratios. The spatial scan statistics uses the Monte Carlo simulation to evaluate the statistical significance of the most likely spatial cluster. The simulated P value of the statistics was obtained through 9999 simulations with the significance level of 0.05 by using the scan statistics.

RESULTS

According to the Ministry of Health database, 43868 CL cases are recorded in the period of 1988-2006 (24). 24312 of these cases are recorded in the period of 1996-2006. The morbidity values (1:100000) are shown in Figure 1. There are fluctuations in the morbidity of CL in the time according to the records. Recent years, there is an increase after the decrease in the 2001 according to the records.

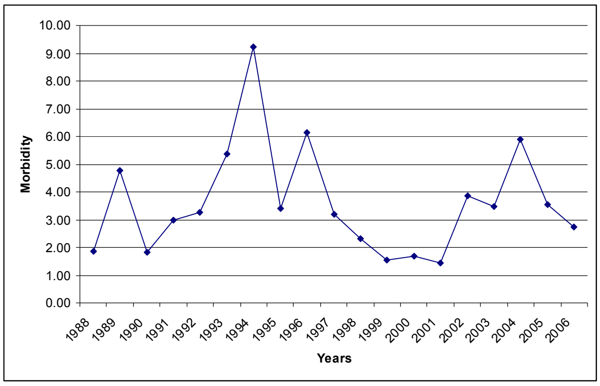

Figure 1. The morbidity values (1:100000) of CL in Turkey for the 1988-2006 period

Firstly, Turkish provinces of Adana, Aydın, Antalya, İçel, Kilis, Şanlıurfa, Hatay, Kahramanmaraş, Niğde, Kayseri and Diyarbakır were determined as the upper outlier cities with 3.0 interquartile extreme rates with CL as a result of descriptive box plot analyses which are useful for describing the general characteristics of the distribution of CL, and for revealing specific provinces with high levels of disease. However, box plot analyses are limited to identify any significant spatial clustering of CL rates. So that, these rates of incidence explored by using spatial rate smoothing analysis. Smoothed average rates of CL (1:100000) according to the provinces of Turkey for the 1996-2006 period as shown in Figure 2.

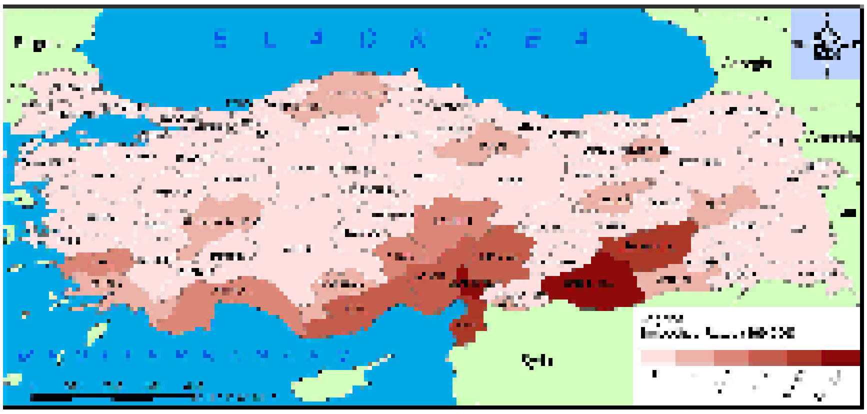

Figure 2.
Choropleth Map of incidence rates of CL (1:100000) according to the provinces of Turkey for the 1995-2006 period.

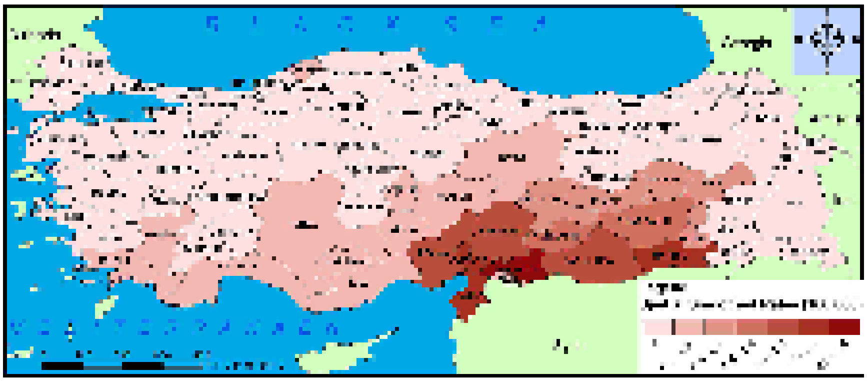

Figure 3.
Choropleth Map of spatial [illegible] smoothed rates of CL according to the provinces of Turkey for the 1995-2006 period.

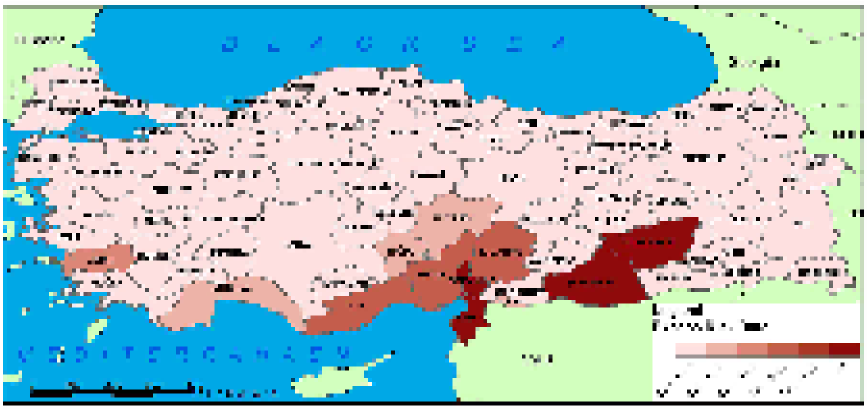

Figure 4.
Choropleth Map of [illegible] values for CL according to the provinces of Turkey for the 1995-2006 period.

Figure 5.
Choropleth Map of CL clusters with [illegible] clustering methods according to the provinces of Turkey for the 1995-2006 period.

Table 1. Global spatial autocorrelation values of cutaneous leishmaniasis

Disease	Moran's I	Expected Index	Z Score	Variance	Observed G	Expected G	Z Score	Geary's C	Z Score
Cutaneous Leishmaniasis	0.0103	-0.013	2.03	0.00013	0.474	0.255	2.11	1.005	0.208

After data smoothing were constructed, a spatial rate smoother based on the notion of a spatial moving average was constructed for explorative spatial data analysis using GeoDA software. Spatial rate smoother doesn't compute an estimate as the raw rate for each area. Instead, it computes for that area together with a set of reference neighbors (15). The purpose of integrating spatial rate smoother method is to emphasize global variations and trends in the data. Thirdly, rates of incidence (with spatial rate smoother) showed that there seems to be a clear trend towards to the southeast region of Turkey (Figure 3).

Each map is a choropleth map where the natural break method for classification of the data has been applied to reflect the distribution best. The natural break technique creates ranges according to an algorithm that uses the mean of each range to distribute the data more evenly across the ranges. Furthermore, a commonly used concept in rate analyses is the excess risk rate and it was used in the determination of risky provinces. The excess risk ratio is the ratio of the observed morbidity rates to the average morbidity rates computed for disease. This average is not the average of the provincial rates, but calculated as the ratio of the total sum of disease. An excess risk rate greater than 1.0 indicates that more disease observed than would have been expected while a ratio of less than 1.0 indicates fewer diseases than expected. According to excess risk rates, Hatay, Osmaniye, Şanlıurfa and Diyarbakır provinces have high risk rates, and seem to problematic areas (Figure 4).

The excess risk is a non-spatial measure, which ignores the influence of spatial autocorrelation. Global spatial autocorrelation analyses showed the presence of spatial clustering of CL in the provinces. There was a high global spatial autocorrelation with CL determined by Moran's I. Geary C could not determine a significant value of global clustering. Global spatial autocorrelation values and the values of significance are shown in Table 1. As shown in Table 1, Getis-Ord General G index (0.474) also showed a significant clustering of high CL morbidity rates.

Finally, using local methods we attempted to show where the clusters are. Choropleth map of local auto correlation values with LISA and G_i* statistics are shown in Figure 5.

Legend shows the LISA statistics results in the form of high-high, low-low, low-high, high-low. Significant clusters ($p<0.05$) determined with G_i* statistics were shown border with green color. Provinces determined as clusters by the maximum likelihood ratio statistics used in scan test were shown with underlined labels.

According to local spatial autocorrelation analysis, Adana, Kahramanmaraş, Osmaniye, Hatay, Şanlıurfa, Adıyaman, Kilis and with G_i* statistic, Adana, Kahramanmaraş, Osmaniye, Hatay and Şanlıurfa, with LISA are determined as endemic regions significantly whereas Adana, Kahramanmaraş, Osmaniye, Hatay, Şanlıurfa, Adıyaman, Kilis, Diyarbakır, Elazığ, Malatya, Niğde, Nevşehir, Kayseri, Sivas, İçel, and are determined as endemic regions by the maximum likelihood ratio statistics used by SaTScan.

DISCUSSION

Two types of leishmaniasis caused by *Leishmania* have been shown in Turkey: CL caused by *leishmania tropica* and visceral leishmaniasis caused by *leishmania infantum,* transmitted by biting sand flies (25). CL is among the six most important infected parasitic diseases of the world in which the transmission profile includes landscape elements and environment (26). Urbanization and migration are important risk factors for CL (27).

CL is the most common type of leishmaniasis in Turkey and is called as Beauty Scar, Oriental Sore, Allepo Sore or Annual Sore by the local people of Turkey (7). In this study, exploratory spatial analyses and spatial cluster analyses were performed for determination of the clustering of CL infections. In addition, this study constitutes the first report on spatial analyses of CL in Turkey.

Specifically, the distributions of CL reports belong the 1996-2006 period were mapped from different aspects such as raw rate, spatial smoothed rate, excess risk rate, and five common provinces were determined statistically significant geographical areas with all spatial clustering methods. Different methods were used for cluster analyses. Almost all methods gave the same results. The key concept is construction of weight matrices for methods. Therefore, some different clusters are determined with the methods.

Adana, Osmaniye, Kahramanmaraş, Hatay, and Şanlıurfa provinces were the common provinces determined as cluster with all methods. Each cluster had a high rate of CL following data smoothing. The smoothed rate data provided more accurate visual representations of the overall distribution of the standardized rates compared with the original maps of observed raw incidence rates.

According to the results of spatial analyses, the presence of CL hotspots in Turkey showed that CL is still a significant public health problem in Turkey. Spatial analyses and statistics significantly contributed to determine the endemic CL.

The epidemiology of the CL is strongly correlated with the ecology, temporal and geographical distribution of the vector, and the reservoir. The activities of the sand fly are strongly correlated with the level of rainfall and temperature. The presence of infected rodents in the area, extensive land reclamation, and irrigation practices that might have caused unnatural moist soil, lead to an increase in the density of sand fly populations (28).

It is thought that most important factor affects the provinces, which determined as endemic by clustering methods, is GAP project (Güneydoğu Anadolu Projesi-GAP). GAP a large ongoing irrigation project, including dams and irrigation channels, has dramatically changed the density of population, climate, land use, and cropping patterns in the Southeastern Anatolia Region (7). Many researchers have reported an increased risk for malaria and CL because of the GAP project (7, 29, 30).

Şanlıurfa, at the center of GAP as capital province of the region is detected as cluster by all methods. GAP is a very big project covering the 9.7% area of Turkey. Twenty percent of irrigable fields of Turkey are in this area of project (31).

Second factor; ninety percent of cutaneous leishmaniasis infections develop in Afghanistan, Syria, Pakistan, Saudi Arabia, Algeria, Iran, Peru, and Brazil (32). Syria and Iran are also neighbors with Turkey at the south.

The first study targeting the CL was initiated in 1995 with the collaboration of Yale (USA), Hebrew (Israel), Ege, Çukurova, Dicle, Gaziantep and Harran (Turkey) universities in the initial stage of GAP project in the region. At the end of this project, the varieties of parasites and flies were determined causing the CL and advices for prevention of disease and individual hygiene measures were applied (33). As a result of these precautionary measures and provisions, morbidity ratios of CL decreased until 2001 as shown in Figure 1. After this year an increase has occurred.

According to the investigations carried out in the region, the majority of patients (70%) were less than 20 years of age, with the highest percentage of (42%) occurring in the 5- to 14-year age. Local studies also indicate much higher CL rates in the GAP region, which is worse than the records of the Ministry of Health (34, 35).

Consequently, CL is still a serious public health problem. High rates in younger people indicate the need of special precautionary cares and measures for this group of age. It is taught that, improvement in health education and studies of mass screening for infections towards to the children at school age will help early diagnosis and treatment, and a decrease at the incidence of CL. A more effective sandfly control through residual insecticide spraying of the houses and the use of insecticide-impregnated bed nets is needed in this region.

Clustering of CL is also a chance for diagnosis and treatment of illness as well as taking precautionary measures. High rates of CL determined by spatial analyses indicated the importance of the services for urgent diagnosis of the illness. Therefore, it is very important to use of such GIS aided spatial analyses as a component in the epidemiologic description and risk assessment of CL to implement specific and geographically appropriate risk-reduction programs.

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