Spatiotemporal Variability of Zoonotic Cutaneous Leishmaniasis Based on Sociodemographic Heterogeneity. The Case of Northeastern Iran, 2011–2016

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SUMMARY: Zoonotic cutaneous leishmaniasis (ZCL) is one of the most prevalent zoonoses in Iran, especially in central and northeastern Iran. This research aimed to examine whether there were spatiotemporal clusters of ZCL cases, and if so, whether there were differences in clustering according to age, sex, area of residence, and occupation. Spatial analysis, including global and local spatial autocorrelations, inverse distance weighting, and space-time scan statistics, were used to determine potential clusters in the villages of Golestan from 2011–2016. Several spatially significant (p < 0.05) clusters were observed in the north and northeastern regions, and most persisted until the last year of the study period. Children (0–10 years) living in rural settings were more likely to have an infection than those living in other areas. Although the disease was centered in the northern regions, housekeepers, females, and patients aged 21–30 and 41–50 years were found to be the high-risk groups in the southern areas. The seasonal pattern indicated that the outbreak mainly began in late summer, peaked in October, and diminished in December. By exploring spatiotemporal variations of ZCL by sociodemographic information, this study was able to identify priority areas for decision-makers in healthcare and resource allocation.
in visceral leishmaniosis (16). Studies on other diseases have also suggested that future epidemiological efforts should examine potential factors that affect disease clusters (22,23). Identifying high-risk areas for susceptible groups can be used as a guideline for local health authorities to more equitably allocate health resources during ZCL epidemics to control and reduce the severity of the outbreak. Extensive studies on ZCL have examined the heterogeneity of spatial and temporal factors but have not explicitly investigated spatiotemporal differences within clusters according to the cases’ sociodemographic information (16,24–26).

To address this research gap, this study utilized spatial analysis and space-time scan statistics to determine spatiotemporal differences within ZCL clusters according to age, sex, area of residence, and occupation in the villages of Golestan province between 2011 and 2016. In addition, unlike previous studies that have examined only a few epidemiological aspects of the disease (27–29), this study described more of the clinical signs. The findings of this study may assist health policymakers in better understanding how sociodemographic factors may affect inhabitants’ health in endemic areas of the disease in order to optimize resource allocation for at-risk groups.

MATERIALS AND METHODS

Study area: Golestan province is in the northeast of Iran (lying between 36° 30’ to 38° 08’ northern latitude and 53° 57’ to 56° 22’ eastern longitude), as shown in Fig. 1. This province, which has 14 counties, 33 cities, 27 districts, 60 rural districts, and 1,024 villages, is where all our analysis was based. The topography in Golestan is extremely diverse, with a vast range in elevation from -45 m near the Caspian Sea to 3,820 m in the mountains of the Jahan-Nama Forest, resulting in various geographical conditions and climates.

Data Preparation: Demographic data on the 4,335 confirmed cases, including sex, age, occupation, travel status, area of residence, clinical symptoms, date of onset, treatment regimen, simultaneous infections among family members, underlying diseases, and location of infection were supplied by the CDC of Golestan province. We used census data from patients who were referred to the Golestan University of Medical Sciences clinics and whose microscopic test results were positive for Leishmania bodies. The number of clinics in Golestan are limited; therefore, the staff are trained at one site and all data are collected in the same way, which ensures that the registration system of human ZCL is uniform throughout this province. The population of each village was obtained from the 2016 census data from the Statistical Center of Iran. Geospatial data, such as province boundaries (polygons) and the locations of villages (points), were generated from the National Cartographic Center of Iran (NCC). To identify spatial clusters, the ZCL incidence rate was calculated based on Equation 1 to analyze the spatial variation of the disease. The population at risk included people who had the potential to become infected (30). Since the disease occurs in both sexes and across all ages, all inhabitants of each village were assumed to be at risk of developing the disease (exposed population). All analyses were carried out at the village level (point layers).

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\text{Incidence rate} = \frac{\text{number of diagnosed cases in a specified period}}{\text{population at risk in that period of time}} \times 100,000
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For space-time analysis, ZCL records were stratified by sex (2, male and female); area of residence (2, rural and urban); age groups (9, aged 0–10; 11–20; 21–30; 31–40; 41–50; 51–60; 61–70; 71–80; > 81); and occupation (10, child, driver, employee, housekeeper, farmer, military (i.e., member of the armed forces), student, worker (i.e., a social group that consists of people who do physical work to get money), unemployed, and other).

Methodology: The epidemiological and temporal characteristics of the ZCL cases in the study area were described. Inverse distance weighting interpolation
was used to predict the distribution of the incidence rate across the province (31). Global and local spatial clustering approaches were carried out using the Moran’s I index and Getis-Ord Gi* statistic, respectively.

The global Moran’s I index explores overall spatial autocorrelation, indicating whether a general pattern of the disease is clustered, random, or dispersed, according to the location of each village and its incidence rate at the same time (32).

Moran’s I index, since it is a global approach, cannot illustrate the structure of the disease clusters locally. Therefore, the Getis-Ord Gi* statistic was chosen to identify the spatial clusters of high and low values (hot spots and cold spots, respectively) (33).

To examine space-time clusters, the space-time scan statistic developed by Kulldorff (34) was employed. Previous studies have applied this statistic to assess clusters of influenza (35) and Ebola (36). A cylinder was used to scan high rate areas. The base of the cylinder refers to the spatial domain, and its height corresponds to the temporal dimension (37). The number of observed cases was compared to the number of expected cases through the calculation of the space-time permutation model (37). A cluster is a cylinder whose number of observed cases is statistically significantly larger than the expected value.

Ethics approval and consent to participate: Since private information of human records was not used for our study, it was not collected. Thus, preparing ethical approval was not necessary.

RESULTS

Demographic characteristics: Over the study period, males were infected more than females (55.98% vs. 44.02%, respectively). However, this difference was minimal in 2016 since the number of infected females increased compared to the first five years of the study period, as shown in Fig. 2-A. Around 92% of the cases were aged ≤ 50 years, and cases aged < 10 years were found to be a high-risk group (40/78%), as shown in Fig. 2-B. The age distribution of males and females was not equal. Of the females, 47.06% were aged ≤ 10 years, whereas only 35.85% of males were in this age group. Fig. 2-C shows, categorized by age group, the cases diagnosed annually. Regarding occupation, the majority of patients were children (33%), followed by housekeepers (19%) and students (17%) (Fig. 2-D). Most cases resided in rural areas (80.88%), and the rest inhabited urban regions. Less than 1% of all patients (0.39%) had a history of ulcers. Less than 50% (41.6%) of the cases had travelled to endemic areas. Regarding the number of lesions, most of the cases (92.13%) had 0–5 ulcers. A total of 2,952 cases (68.10%) were treated with a systemic glucantime regimen. Of the 4,335 patients, 1,660 (38.29%) had family members who were simultaneously infected. Most cases did not have underlying diseases (98.03%).

Temporal trends: The incidence of cases according to year and month were diverse throughout the study period (Fig. 3). From 2011 to 2013, the annual number of cases decreased, reaching a minimum of 605 in 2013 then increased to a maximum of 920 in 2016. Overall, a growth rate was observed over the 6-year study period. A seasonal trend was observed, as the ZCL outbreak started in July, peaked in October, and waned in December during the six years (Fig. 3).

Spatial analysis: The results of Moran’s I and its z-scores, which ranged from 4.02 to 13.22, are displayed...
in Table 1. These prove the high level of ZCL clustering throughout the study area in the 6-year period. As the high z-score values suggest, the spatial pattern of the disease did not follow a stochastic distribution.

To determine high- and low-risk areas, the outputs of the hot spot analysis were interpolated using the inverse distance weighting method (Fig. 4). The results indicated that statistically significant hot spot areas (black) were located in north and northeastern Golestan. Further, statistically significant cold spot areas (white) were mainly concentrated in the south, west, and central parts of the province. Additionally, most of the hot spot regions were aggregated in rural areas.

**Spatiotemporal analysis**: Spatiotemporal scan statistics for ZCL cases in the total population of the Golestan villages detected eight significant clusters (Table 2). The most likely cluster, which had the maximum likelihood ratio test statistic, consisted of 3 villages located in the northeast areas of the province (Fig. 5). The secondary clusters were mainly concentrated in the northern and northeastern regions of the province. The most likely cluster persisted for a longer period (1 year) than the other clusters (Table 2). Eight significant clusters were detected for males (Table 2). The most likely cluster for males consisted of 6 villages located at the common border of Gonbad Kavus, Maraveh Tappeh, and Kalaleh counties (Fig. 5). This cluster closely mirrored that of the total population.
in terms of location, time, and size. The first secondary cluster for females persisted from late-2011 to mid-2014 and encompassed a large area in some highly populated counties in the south of the province (Fig. 5).

According to the area of residence, the clusters for the rural population were similar to the clusters for the total population, albeit with a slight difference. This can be attributed to the density of the rural areas. Only two significant urban clusters were observed in highly populated cities in the north and south of the province (i.e., Gonbad Kavus and Gorgan, respectively).

Clusters related to age groups 0–10, 11–20, and 31–40 were mostly concentrated in the northern and northeastern regions of the province, whereas clusters for age groups 21–30 and 41–50 were observed in the south of the province. There were no significant clusters observed for the age groups older than 50 years because there were very few ZCL cases in these groups.

The most likely cluster observed for children consisted of 39 villages in Gonbad Kavus county, which persisted from late-2014 to mid-2015. The most likely cluster for drivers was found in Aq Qala county in late 2016. The most likely cluster for the employee group was detected in the same region as the worker group, but persisted for different periods (Fig. 5 and Table 2). A most likely cluster was also observed for the military group, which consisted of 68 villages located in the north of the province where most of the province’s garrisons were located. The most likely cluster for housekeepers was similar to the first secondary cluster for females. Students had a most likely cluster that was reasonably concordant with the most likely cluster for the total population. No significant spatiotemporal clusters were detected for the unemployed group or the other occupations.
Table 2. Summary of statistically significant spatiotemporal clusters of ZCL cases in the study area, during 2011-2016 by demographic characteristics

| Category | Cluster | Start Date | End Date | No. of Villages | Radius | No. of Observed Cases | No. of Expected Cases | Test Statistic | P-value<sup>1</sup> |
|----------|---------|------------|----------|-----------------|--------|-----------------------|---------------------|---------------|-----------------|
| All populations | Most likely cluster | 2013/10/1 | 2014/10/31 | 3 | 5.472603341 | 88 | 27.5727797 | 42.12331459 | 1.67E-15 |
| | Secondary cluster 1 | 2014/11/1 | 2015/1/31 | 69 | 16.21769292 | 55 | 13.0519031 | 37.36809313 | 2.2704E-13 |
| | Secondary cluster 2 | 2015/6/1 | 2015/8/31 | 23 | 13.32524377 | 47 | 11.73587082 | 30.09247092 | 4.0184E-10 |
| | Secondary cluster 3 | 2016/8/1 | 2016/11/30 | 11 | 20.2653098 | 119 | 56.79584775 | 26.2698454 | 2.0445E-08 |
| | Secondary cluster 4 | 2015/10/1 | 2015/10/31 | 75 | 24.13707438 | 55 | 20.01822376 | 20.74836565 | 5.9639E-06 |
| | Secondary cluster 5 | 2012/11/1 | 2012/12/31 | 2 | 7.227451164 | 15 | 1.972318339 | 17.42453044 | 0.000181696 |
| | Secondary cluster 6 | 2016/9/1 | 2016/11/30 | 6 | 7.33018005 | 55 | 22.70634371 | 16.48545239 | 0.000476993 |
| | Secondary cluster 7 | 2012/10/1 | 2013/1/31 | 39 | 43.63176139 | 30 | 8.879584775 | 15.4540209 | 0.001375822 |
| Female | Most likely cluster | 2014/9/1 | 2014/10/31 | 6 | 7.407412297 | 46 | 13.7058964 | 23.62065021 | 1.1017E-07 |
| | Secondary cluster 1 | 2011/10/1 | 2014/6/30 | 340 | 57.98402996 | 126 | 66.98113208 | 21.55314959 | 4.62104E-07 |
| | Secondary cluster 2 | 2014/11/1 | 2015/1/31 | 46 | 14.70286038 | 26 | 6.11259329 | 17.85973308 | 2.7798E-05 |
| | Secondary cluster 3 | 2012/11/1 | 2013/9/30 | 7 | 18.80007231 | 27 | 8.452830189 | 12.89973335 | 0.006792107 |
| | Secondary cluster 4 | 2015/7/1 | 2015/8/31 | 23 | 13.32524377 | 19 | 4.635220126 | 12.4931332 | 0.01033256 |
| | Secondary cluster 5 | 2015/10/1 | 2015/10/31 | 73 | 23.57141058 | 26 | 8.254716981 | 12.16795987 | 0.013 |
| | Secondary cluster 6 | 2015/9/1 | 2016/11/30 | 8 | 17.64603857 | 77 | 41.9496553 | 12.04569923 | 0.014 |
| | Secondary cluster 7 | 2013/1/1 | 2013/7/31 | 83 | 14.38458463 | 5 | 0.187106918 | 11.62074775 | 0.027 |
| Rural | Most likely cluster | 2013/10/1 | 2014/10/31 | 3 | 5.472603341 | 88 | 27.3511228 | 42.1791291 | 1E-17 |
| | Secondary cluster 1 | 2014/11/1 | 2015/1/31 | 69 | 16.21769292 | 55 | 12.91049329 | 37.87637093 | 3E-15 |
| | Secondary cluster 2 | 2015/6/1 | 2015/8/31 | 23 | 13.32524377 | 47 | 12.70678836 | 27.35219594 | 5.7693E-10 |
| | Secondary cluster 3 | 2016/8/1 | 2016/11/30 | 11 | 20.2653098 | 119 | 56.79584775 | 26.2698454 | 2.0445E-08 |
| | Secondary cluster 4 | 2011/9/1 | 2014/7/31 | 205 | 40.66201301 | 175 | 102.4346384 | 21.93690785 | 3.0265E-07 |
| | Secondary cluster 5 | 2012/11/1 | 2012/12/31 | 2 | 7.227451164 | 15 | 2.032230462 | 17.04000013 | 8.7153E-05 |
| | Secondary cluster 6 | 2016/9/1 | 2016/11/30 | 6 | 7.33018005 | 55 | 23.58471192 | 15.29723707 | 0.000653989 |
| | Secondary cluster 7 | 2012/10/1 | 2012/12/31 | 34 | 43.01088978 | 20 | 4.665861869 | 13.79978049 | 0.003689825 |
| | Secondary cluster 8 | 2012/10/1 | 2013/11/30 | 16 | 8.60171154 | 29 | 9.38106138 | 13.16568928 | 0.00766718 |
| | Secondary cluster 9 | 2011/6/1 | 2011/9/30 | 3 | 15.45398796 | 22 | 5.84978323 | 13.03965996 | 0.008864325 |
| Urban | Most likely cluster | 2014/9/1 | 2016/12/31 | 259 | 71.9202948 | 161 | 106.3908323 | 14.20821573 | 6.2375E-05 |
| | Secondary cluster 1 | 2011/12/1 | 2014/9/30 | 486 | 68.48755296 | 187 | 134.9831122 | 10.93739207 | 0.002876629 |
| Age          | Cluster          | Start Date      | End Date      | Cases | Age Range | Incidence | Incidence CI | Prevalence | Prevalence CI |
|--------------|------------------|-----------------|---------------|-------|-----------|------------|--------------|------------|--------------|
| 0-10         | Most likely      | 2013/10/1       | 2014/10/31    | 6     | 7.407412297 | 53         | 16.83257919 | 24.99837638 | 4.45603E-09  |
|              | Secondary cluster 1 | 2016/8/1       | 2016/11/30    | 11    | 20.2653098   | 87         | 45.45475113 | 54.4393012  | 0.00213579  |
|              | Secondary cluster 2 | 2011/4/1       | 2011/8/31     | 154   | 26.92268145  | 32         | 10.25       | 14.8157858  | 0.00043107  |
|              | Secondary cluster 3 | 2015/10/1      | 2015/11/30    | 11    | 9.60069333   | 26         | 7.496606335 | 13.92889856 | 0.001172085 |
|              | Secondary cluster 4 | 2012/7/1       | 2013/9/30     | 6     | 17.53060201  | 96         | 54.31561086 | 15.50225189 | 0.001895646 |
|              | Secondary cluster 5 | 2013/2/1       | 2013/9/30     | 32    | 8.950933813  | 10         | 1.191176471 | 12.48960868 | 0.005925604 |
|              | Secondary cluster 6 | 2011/11/1      | 2012/4/30     | 147   | 23.17099613  | 8          | 0.778280543 | 11.43393453 | 0.018       |
| 11-20        | Most likely      | 2015/10/1       | 2015/10/31    | 14    | 10.99970004  | 14         | 2.804347826 | 11.4064532  | 0.013083839 |
|              | Secondary cluster 1 | 2013/10/1      | 2013/11/30    | 22    | 6.217657759  | 11         | 1.739130435 | 11.09132681 | 0.013       |
|              | Secondary cluster 2 | 2011/4/1       | 2011/12/31    | 39    | 13.04810148  | 13         | 2.555072464 | 10.78412074 | 0.025       |
| 21-30        | Most likely      | 2012/10/1       | 2013/4/30     | 72    | 20.86408721  | 15         | 3.03443776  | 12.0963136  | 0.005225098 |
|              | Secondary cluster 1 | 2011/11/1      | 2011/12/31    | 50    | 13.48948081  | 7          | 0.505102041 | 11.93443166 | 0.006361212 |
| 31-40        | Most likely      | 2011/5/1        | 2011/9/30     | 46    | 28.73899283  | 15         | 3.221006565 | 11.4505681  | 0.00429725  |
|              | Secondary cluster 1 | 2013/12/1      | 2015/1/31     | 39    | 19.29725235  | 18         | 5.133479212 | 9.9010109   | 0.026       |
| 41-50        | Most likely      | 2013/2/1        | 2014/5/31     | 265   | 42.57193848  | 21         | 6.98630137  | 9.44860142  | 0.029       |
| Childhood    | Most likely      | 2014/10/1       | 2015/7/31     | 39    | 21.11933579  | 44         | 15.79081272 | 17.166602   | 2.32909E-05 |
|              | Secondary cluster 1 | 2013/10/1      | 2014/9/30     | 6     | 7.407412297 | 30         | 8.662897572 | 16.0903068  | 7.84104E-05 |
|              | Secondary cluster 2 | 2012/7/1       | 2013/9/30     | 8     | 16.7103049   | 83         | 47.03038869 | 11.6553591  | 0.01157535  |
| Driver       | Most likely cluster | 2016/10/1   | 2016/11/30    | 32    | 15.29351313  | 6          | 0.685714286 | 7.83776369  | 0.011       |
|              | Secondary cluster 1 | 2012/6/1       | 2012/7/31     | 18    | 8.07446983   | 5          | 0.476190476 | 7.332406106 | 0.033       |
| Employee     | Most likely cluster | 2013/9/1      | 2013/10/31    | 49    | 37.60357058  | 6          | 0.965517241 | 6.15563729  | 0.018       |
| Farmer       | Most likely cluster | 2011/12/1     | 2013/11/30    | 194   | 27.04182376  | 19         | 5.507614213 | 10.522361   | 0.00277992  |
| Housekeeper  | Most likely cluster | 2011/9/1      | 2013/10/31    | 346   | 65.65921493  | 91         | 47.11217814 | 17.2609094  | 1.3853E-05  |
|              | Secondary cluster 1 | 2014/9/1       | 2014/10/31    | 17    | 15.1949038   | 15         | 2.718377088 | 13.42934213 | 0.00124714  |
| Military     | Most likely cluster | 2011/4/1      | 2012/9/30     | 68    | 52.19161851  | 29         | 7.82771536  | 17.6920782  | 2.03796E-07 |
| Student      | Most likely cluster | 2013/10/1     | 2014/10/31    | 3     | 5.472603341  | 34         | 10.2367688  | 17.4296961  | 4.09126E-06 |
|              | Secondary cluster 1 | 2014/11/1     | 2014/12/31    | 39    | 13.04810148  | 13         | 1.516713092 | 16.53841184 | 1.26753E-05 |
|              | Secondary cluster 2 | 2015/11/1     | 2016/10/31    | 43    | 39.1372527   | 59         | 28.66295265 | 12.93450682 | 0.001091803 |
| Worker       | Most likely cluster | 2012/11/1     | 2012/12/31    | 29    | 32.53337497  | 6          | 0.502793296 | 9.421290301 | 0.047       |

1) Statistical significance was calculated based on a Monte Carlo simulation of 999 repetitions and statistical significance at 0.05.
This study indicates the existence of spatiotemporal agglomerations of ZCL cases according to sociodemographic factors in Golestan. The result of Moran’s I index revealed that the ZCL incidence rate in villages of Golestan province had global spatial autocorrelation (clustered) over the study period. In addition, the hotspot analysis highlighted high and low endemic areas, which local health authorities can utilize as a substantial guideline to more equitably allocate health facilities to endemic areas during epidemics.

Based on the results of the space-time scan statistics, most likely clusters were significantly associated with areas in the north and northeastern regions of the province, confirming the results of the hot spot analysis. Previous investigations in this province have had similar findings (26,38). Moreover, these clusters were found to occur in the last months of a year, especially in October, which is in line with the temporal trend observed in this study.

Children less than 10 years old living in the northern and northeastern regions of the province have more exposure to infection. Although the disease is more common in the northern areas of the province, the existence of highly significant clusters for housekeepers, females, and patients aged 21–30 and 41–50 years in the southern regions requires further attention from health officials. Consistent with the literature (18,26), the rural population was found to be at higher risk of exposure to the disease than urban inhabitants. Although there are studies that have identified clusters of the disease in space and time (16,24–26), many of them have not explicitly examined space-time clusters for patients based on sociodemographic factors.

By tracking the hotspots, this study demonstrated the dynamics of ZCL throughout the study area, as shown in Fig. 4. Infection aggregation moved from the north toward the northeast and east in the first three years of the study period, and then emerged in the northern and central regions of the province. The displacement of high infection areas was likely a result of environmental changes, which caused vectors and reservoirs to migrate, and, in turn, caused movement in case aggregation (39).

The temporal pattern found in this study was partially consistent with the seasonal trend of ZCL found in previous studies (9,40). Since the incubation period of the disease is approximately four months, and the maximum activity of sand flies in the studied area lasts from mid-spring to the end of summer (9), it was expected that most cases would occur in the Fall. This can be observed in the seasonal pattern obtained in this study. It is worth noting that preventive measures to control and reduce the number of cases, such as using insecticides and protective nets, should be taken at the beginning of the warm season, since this corresponds to the significant increase in sand flies in the study area.

Based on demographic results, children aged ≥ 10 years were identified as the most at-risk group. This could be because older people are likely to have been exposed to the infection at least once during their lifetime and thus obtained lifelong resistance and higher herd immunity (41). This partially corresponds to the results of the ulcer history in this study. During the study period, ZCL was more common in males than in females, but this difference reached its minimum in the last year of the study period (18,42,43). Although sex hormones can affect immunity to the disease (44), there is no convincing explanation for this difference. However, behavioral characteristics, such as men’s habit of covering less of their bodies than women in the warm months, may make them more susceptible to
sand fly bites than women (26). The proportion of ZCL cases aged ≤ 10 years gradually increased from 32% in 2011 to 51% in 2016, suggesting that health authorities should pay close attention to this high-risk group.

This study may help epidemiologists and public health officials to understand where, when, and why this disease occurs in order to fine-tune screening programs, which highlights the value of epidemiological surveillance in the field of medical geography. To extend previous studies, this detailed investigation not only described the spatial and temporal trends of ZCL by demographic factors, but also explained the epidemiological aspects of the disease in the studied area. According to the results of the present study, it can be concluded that ZCL is becoming a grave public health problem in Golestan province, especially in the north and northeast areas identified as hot spots. The clusters detected by sociodemographic characteristics varied significantly, revealing areas where health center resources may be inadequate. More studies need to be carried out to explore the reasons the detected clusters exist, especially in the southern regions of the province where high-risk clusters were observed for housekeepers, females, and patients aged 21–30 and 41–50 years. Meanwhile, to establish control strategies, this research could serve as a foundation to detect how the behavior of this disease changes over time, space, and demographic factors. In addition, the seasonal pattern observed can serve as an efficient tool for early warning systems to be developed to prevent outbreaks. Additionally, by identifying disease-prone regions, health insurance institutions can adjust payment plans for high-risk groups.

The current study has limitations that may impede the explicit characterization of the spatiotemporal pattern of the disease. First, the healthcare surveillance system for ZCL patients in Iran is passive, and only information concerning cases who refer to health centers for treatment are recorded, thus the underreporting of cases in our study is a concern. Since ZCL spread depends on determinants related to climate, the ecology of the area, environmental changes, the culture (45), and information about reservoirs and vectors, exploring these may provide a more realistic viewpoint of the spatial and temporal pattern of ZCL to mitigate spatial inequalities caused by the disease.

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Conflict of interest None to declare.

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