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Spatial and demographic aspects of kala-azar (visceral leishmaniasis) in Iraq during 2011-2013

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Abstract. Visceral leishmaniasis (kala-azar) continues to be a significant public health issue and socioeconomic obstacle in Iraq. A descriptive study was conducted of confirmed kala-azar patients (n=2787) reported by the Communicable Diseases Control Center (CDCC), Iraq during the 3 year period of 2011-2013. Objectives were to identify possible associations of kala-azar with patient demographics (age, sex) and spatial localities (provincial sources and abiotic factors) as well as to map the disease in Iraq using GIS techniques. Males showed higher risk for kala-azar than females, and the majority of cases were recorded among those individuals <5 years of age. Approximately 40% of cases derived from the eastern provinces (Misan, Wasit and Diyala). Although most cases occurred in regions with moderate annual rainfall and a high rural population, elevation was the most significant explanatory variable when contrasted to rainfall, temperature, humidity and rural vs urban population status. These findings may provide insights for investigators assessing management approaches for the control of kala-azar in Iraq.

INTRODUCTION

Leishmaniasis is a significant burden on human health and society. The incidence of this neglected disease is particularly severe in some of the world's poorest countries. In general, the disease and its causative agents received far less attention than other infectious diseases such as tuberculosis, malaria, and HIV (Antinori *et al.*, 2012), despite its severity. The disease is distributed in 98 countries, and around 1.3 million new cases/year are reported, resulting in an estimated 20,000–40,000 deaths annually (Alvar *et al.*, 2012).

Leishmaniasis is caused by over 20 species of pathogenic intracellular protozoan parasites of the genus *Leishmania*, which are transmitted by the bite of a female phlebotomine sandfly (Kobets *et al.*, 2012). The clinical spectrum of leishmaniasis varies from an auto-resolving cutaneous ulcer (known in Iraq as oriental sore or Baghdad boil), to a mutilating muco-cutaneous disease, to a lethal visceral illness. The visceral form of leishmaniasis, known in parts of Asia and Africa as kala-azar, is a major public health problem in endemic countries and is generally fatal if untreated (Desjeux, 2004).

Leishmaniasis is endemic in Iraq, where both cutaneous and visceral forms of the disease are found. Kala-azar is generally found in central Iraq but extended its range to southeastern parts of the country following the Gulf War. *Leishmania donovani* and *L. infantum*, which are transmitted by *Phlebotomus alexandri* and *P. papatasi* sand flies, are the causative agents (Sacks *et al*., 1985; Salam *et al*., 2014). Domestic dogs (*Canis familiaris*), golden jackals (*C. aureus*) and black rats (*Rattus rattus*) are reported reservoir hosts of the disease in the region (Sukkar, 1986; Sukkar, 1987), and it is likely that *Leishmania* spp. in Iraq cycles between sand flies, reservoir hosts and humans. Human infection likelihood is associated with overlap of human activity patterns and those of reservoir systems (Ashford, 2000). A total of 1,049 cases of visceral leishmaniasis were reported in 2008, down from 3,218 cases in 2004 because of the efforts of the Ministry of Health in Iraq and the World Health Organization (WHO), and 90% of the cases were reported in children. Most of these cases were reported from the eastern provinces of Diyala, Wasit, Misan, and Basrah (Majeed *et al*., 2013).

Iraq covers a diversity of climatic, geographic and population features, some of which may be contributory to the incidence of visceral leishmaniasis. In general, the climate is subtropical, but continental climate regimes occur in northern Iraq. Understanding this climatic and spatial variation is important, as the spatial distribution and seasonality of leishmaniasis in Iraq will likely be affected by climate change (Ready, 2008). This may be especially important in temperate zones where increased average temperatures might permit extension of the breeding seasons of the existing *Phlebotomus* species, or the establishment of tropical and/or subtropical vector species. Such changes might allow the persistence of the pathogen in areas where low temperatures have historically prevented the vector from over-wintering (Gramiccia & Gradoni, 2005).

In this study we used descriptive and GIS approaches at a macro-epidemiological level to identify basic demographic and climatic factors such as temperature, rainfall and elevation that are associated with reported cases of kala-azar in Iraq. The distribution of kala-azar in Iraq has received limited attention, and so even relatively simple spatial mapping of reported cases may be insightful. Thus the overall aim of this study was to analyze data on kala-azar provided by the Communicable Diseases Control Center (CDCC), Bagdad, to illustrate basic spatial and demographic patterns which may be of use in planning future management strategies.

MATERIALS AND METHODS

Study area

We examined the distribution of kala-azar across the entire country of Iraq. Iraq is composed of 18 provinces with a total population of approximately 33 million (CSO, 2013). Total area is 437000 Km^2 between latitudes 29° 5’ and 37° 22’ N and longitudes 38° 45’ and 48° 45’ E. Bordering countries are Iran, Turkey, Syria, Jordan, Saudi Arabia and Kuwait, and each of these countries has a long-history of the presence of the disease.

Visceral leishmaniasis data

In Iraq, kala-azar is a closely monitored disease with diagnoses reported from all provinces to the CDCC, Ministry of Health, Baghdad. Between 2011 and 2013, data from 2787 patients admitted to Iraqi hospitals and diagnosed with kala-azar were gathered by CDCC. Diagnoses of kala-azar were confirmed by one or multiple methods, including rK-39 strip tests, bone marrow or spleen aspiration, microscopic examination and indirect fluorescent antibody tests. For each patient, information was available on sex, age (grouped as <1 yr, 1-4 yrs, 5-14 yrs, and >15 yrs), province, and month of diagnosis.

Predictor variables and statistical analyses

Total population size, rural population size, urban population size, elevation, total annual rainfall, and annual mean temperature for three consecutive years (2011-2013), were derived from Central Statistical Organization annual reports for each province (CSO, 2011; CSO, 2012; CSO, 2013). ArcGIS version 10.3.1 (http:// www.esri.com/arcgis) was used to map geospatial and related climatic and demographic information. The analysis is based on the kriging and inverse distance weighted methods (Setianto & Triandini, 2013).

Spearman's correlation coefficient and multiple linear regressions were used for contrasting the correlations of spatial, climate and population factors on kala-azar incidence (the number of new cases occurring within a period of time) using Statistical Package for the Social Sciences (SPSS Inc, Chicago IL, USA) and R (https://www.r-project.org/) with values of $P < 0.05$ considered statistically significant.

RESULTS

The number of reported cases of kala-azar (total n = 2787) declined by 50.7% between 2011 (n = 1167 cases) and 2013 (n = 575 cases). Nonetheless, in each year there were strong biases towards diagnoses in males and in younger individuals. A greater percent of cases was observed in males (56.3%) in each year, although there was variability in the sex ratio of cases (Table 1). In 2011, there were 1.2 diagnosed males per diagnosed females, with that ratio increasing slightly in 2012 (1.4) and 2013 (1.3). Kala-azar was also observed to be largely a disease of children, with 93% of reported cases occurring among patients < 5 years of age (Table 1). An additional 7% of patients were 5-14 years of age. Across the three year reporting time frame, no cases were recorded in individuals aged >14 years of age. As with the changes in the distribution among males and females across the study period, there was also a change in the distribution of cases among children. In 2011, 40% of cases involved children <1 year of age. This increased to 54% of cases in both 2012 and 2013, with an associated decline in older children from 59% in 2011 to 45-46% in 2012-2013.

Kala-azar patients were reported from 14 of Iraq's 18 provinces (Table 2), with the exceptions being the provinces of Dohuk, Erbil, Suleimaniyah and Ninevha. The majority of the cases were reported in the central eastern region of the country (Figure 1a), with 69.8% of cases reported from the provinces of Qadisiyah, Misan, Wasit, Diyala and Dhi-qar. Each of these provinces accounted for 320-488 of the reported cases for the three year period (Table 1). The high numbers of cases were not a function of greater size, as the per capita rates of occurrence were also higher in these provinces (Figure 1b).

Diagnoses of kala-azar revealed strong patterns of seasonality (Figure 2). In each year, 49-60% of cases were identified during the winter and early spring months of January-March, with peaks in March (2011) or February (2012 and 2013). While the overall decline in the number of kala-azar cases in 2013 relative to 2011 and 2012 (Table 1) was apparent from comparisons of the absolute number of monthly case (Figure 2), the strong seasonal pattern remained in terms of both absolute and proportional (number of cases for each month/the total number of cases for the whole year) numbers of cases. Indeed, despite the >50% decline in the percent of cases occurring between 2011 and 2013, the percent of cases occurring in the non-peak months was similar across years, and especially between the months of June through December.

Statistical analyses revealed significant relation ($p<0.05$) between elevation and the occurrence of kala-azar, with a decrease in elevation correlated to increases in occurrence. Overall, 96.7% of the cases occurred in provinces with an elevation ranging from 3–63 m above sea level (Figure 3a, 3b). Total annual rainfall, annual mean temperature and rural population had no significant relation with occurrence of the disease. Most cases (81%) were reported at provinces with annual rainfall of 38-235 mm while no cases were detected at provinces with total annual rainfall of 442-562 mm (Figure 4a, 4b). Provinces with low mean temperature showed no or low kala-azar cases (Figure 4c), and 95.6% of the total cases were reported in provinces with humidity of 38-45% (Figure 4d). Results also showed that 4.3% of the cases occurred in provinces with 18%-33% of inhabitants classified as rural, while the other 95.7% of cases occurred in provinces with a rural population of 34%-48% (Figure 4e, 4f).

Table 1. Sex and age of 2787 Iraqi kala-azar patients reported between 2011 and 2013

Sex/Age	2011		2012		2013		Total	
	Number	%	Number	%	Number	%	Number	%
Male	630	53.98	612	58.56	327	56.86	1569	56.29
Female	537	46.01	433	41.43	248	43.13	1218	43.7
<1	469	40.18	568	54.35	311	54.06	1348	48.36
1–4	601	51.49	412	39.42	232	40.34	1245	44.67
5–14	97	8.31	65	6.23	32	5.56	194	6.96
>14	0	0	0	0	0	0	0	0

Table 2. The distribution of kala-azar among the Iraqi provinces for the years 2011-2013

Provinces	Number of Cases			Total	Mean	S.D.
	2011	2012	2013			
Anbar	64	80	12	156	52	26.7
Babil	73	61	54	188	62.7	6.9
Baghdad	55	47	39	141	47	5.3
Basrah	41	54	17	112	37.3	13.6
Dhi-qar	169	212	107	488	162.7	37.1
Diyala	181	176	80	437	145.7	43.8
Dohuk	0	0	0	0	0	0
Erbil	0	0	0	0	0	0
Karbala	13	9	7	29	9.7	2.2
Misan	197	80	49	326	108.7	58.9
Muthanna	21	29	20	70	23.3	3.8
Najaf	12	4	6	22	7.3	3.1
Ninevha	0	0	0	0	0	0
Qadisiyah	128	112	80	320	106.7	17.8
Salahuddin	20	7	3	30	10	6.7
Suleimaniyah	0	0	0	0	0	0
Ta'mim	43	45	4	92	30.7	17.8
Wasit	150	129	97	376	125.3	18.9

DISCUSSION

In Iraq, kala-azar is caused by *L. donovani* and *L. infantum* and is endemic although sometimes sporadic in nature. Nonetheless, there was a strong decline in the number of cases recorded in 2013 compared to 2011 and 2012. This decline was likely a function of efforts by both the Ministry of Health in Iraq and the WHO. Most cases were detected in male individuals. This is probably because males are more involved in outdoor activities (Nail & Imam, 2013), especially in Iraq, and therefore are more exposed to sand fly bites. However, given the very young age of most cases, the causative nature of this bias in sex ratio deserves additional attention. This bias is nonetheless consistent with the other studies in Iraq (Nouri & Al-Jeboori, 1973; Gani *et al.*, 2010). Further, as previously noted (Ready, 2008), the overall incidence of kala-azar is far greater among <5 years old compared to other age classes, and no cases were reported from individuals > 14 years of age. This high burden among children could be associated with poor nutrition and an

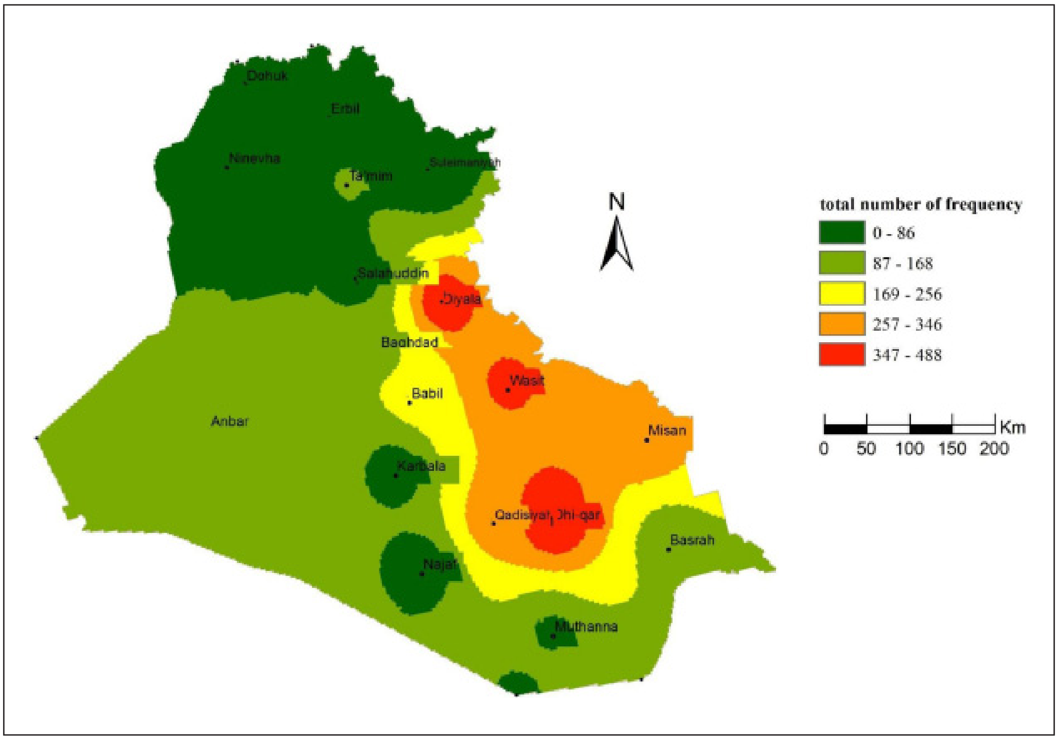

Figure 1a. The distribution and number of cases of kala-azar in Iraq reported between 2011 and 2013 by the Iraqi Ministry of Health Communicable Diseases Control Center.

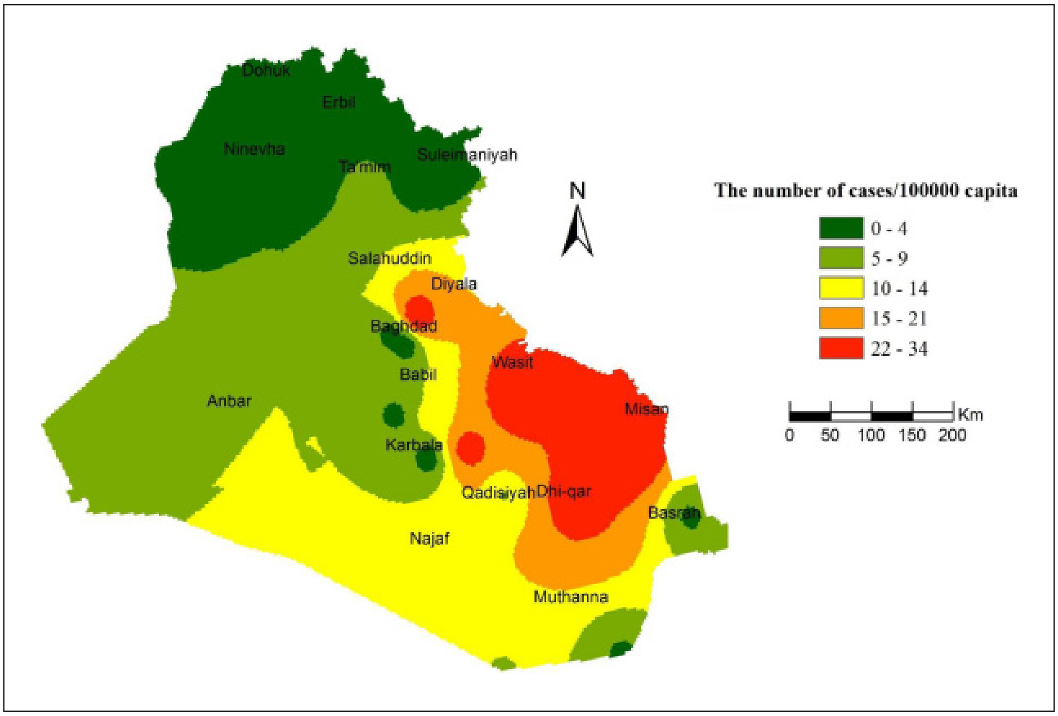

Figure 1b. The number of cases of kala-azar in Iraq per 100000 capita between 2011 and 2013.

Figure 2. The annual pattern of kala-azar across Iraq based on data collected between 2011 and 2013. a): Number of reported cases per month, revealing the decline in cases per month in 2013 relative to previous years. b): The percent of cases (data for each year analyzed independently) reported per month, revealing a peak reporting period of January-March.

immature immune system (Osman, 2011). On the other hand, the decrease in incidence with age may be also be a function of the development of immunity provoked by former infections (Saha *et al.*, 2006).

Kala-azar cases were more common in winter months, with peaks during February-March in each year. The incidence of infection then declined, with relatively low incidence occurring from June through November. This seasonal variation is likely associated with the phenology of the various reservoir species in these areas as well as the activity of the sand fly vectors. Sand fly activity in Iraq is from approximately April through November, with peaks in September-October. Given a typical incubation period for *L. donovai* of 2-6 months, sand fly bites in September or October would result in disease in January or February (Stoops *et al.*, 2013), approximately the period when cases were referred to and confirmed by the CDCC, Baghdad. This result is in agreement with the results obtained for cutaneous leishmaniasis by Jaber *et al.* (2014) and Al-Warid *et al.* (2017).

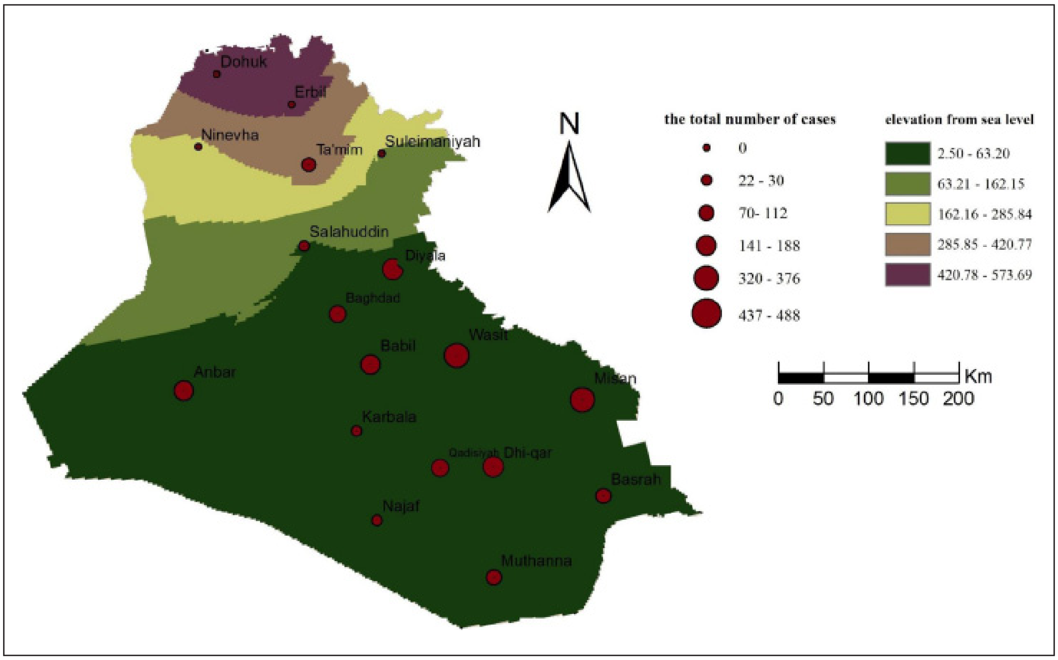

Figure 3a. Reported cases of kala-azar overlaid on an elevation map of Iraqi provinces.

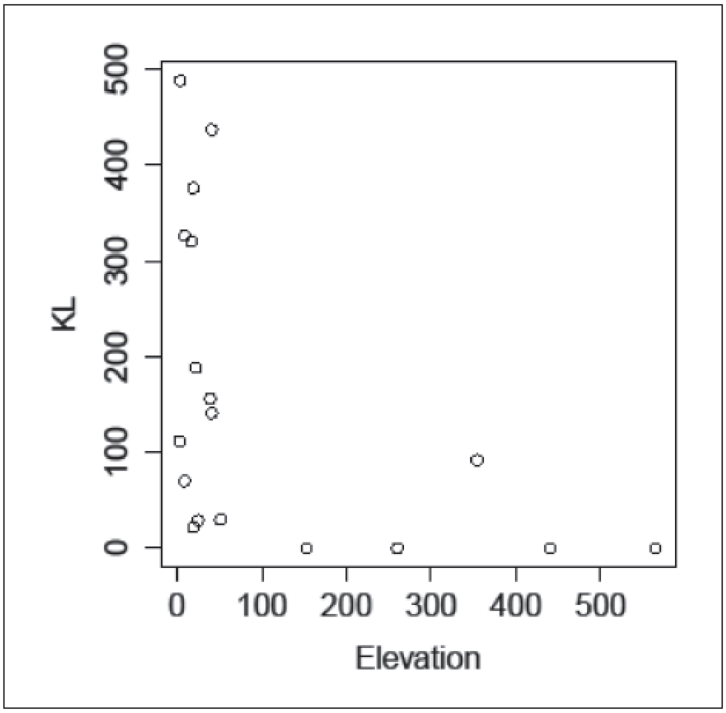

Figure 3b. Association between kala-azar (KL) cases and elevation above sea level; F= 5; P< 0.04.

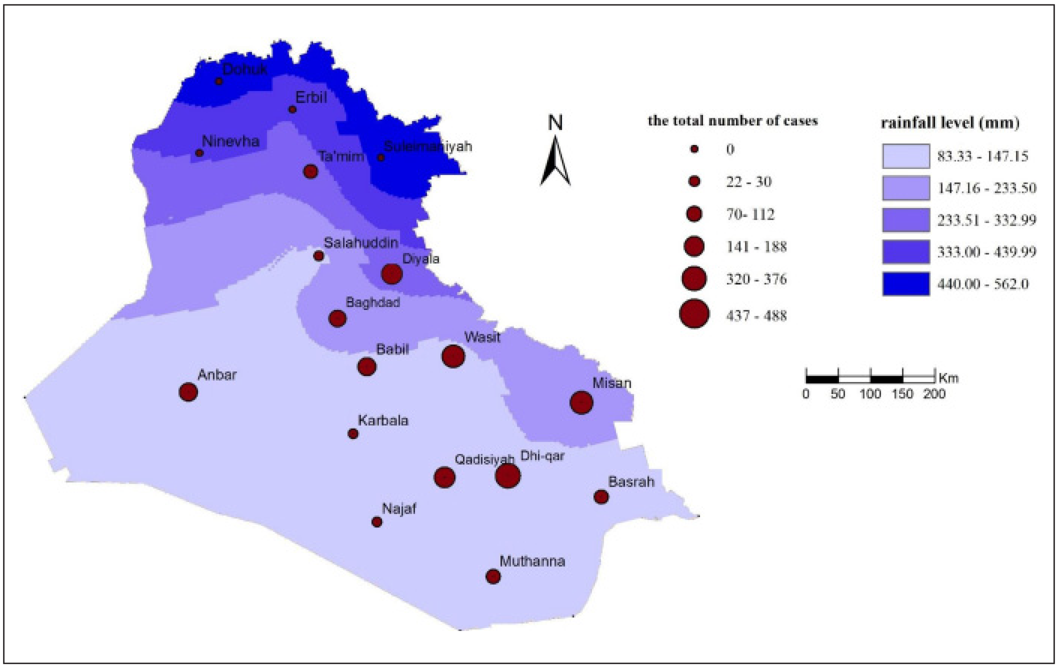

Figure 4a. Reported cases of kala-azar overlaid on an annual rainfall map of Iraqi provinces.

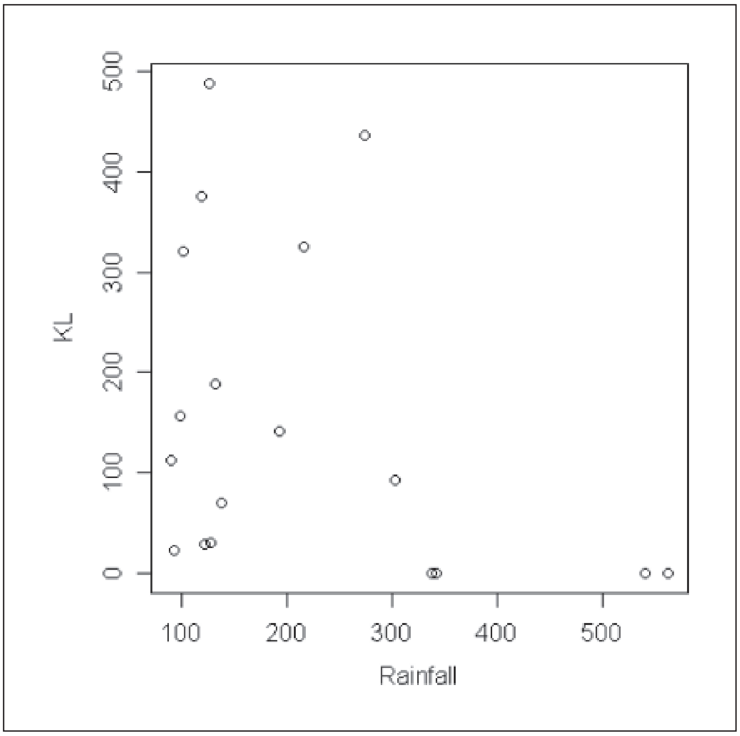

Figure 4b. Association between kala-azar cases (KL) and rainfall; F=2.546; P=0.13.

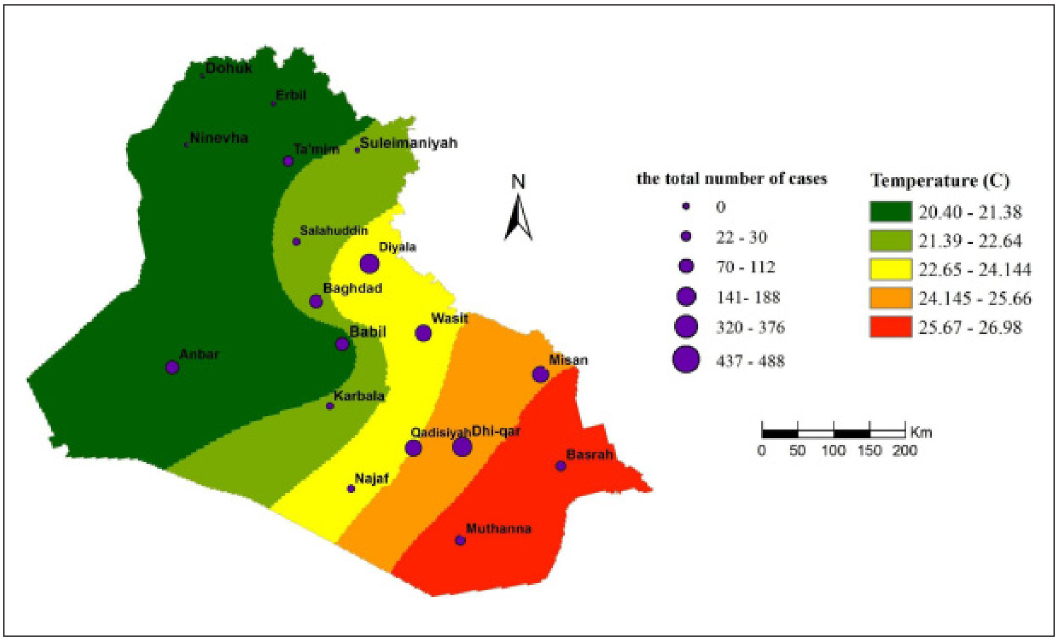

Figure 4c. Reported cases of kala-azar overlaid on an annual temperatures map of Iraqi.

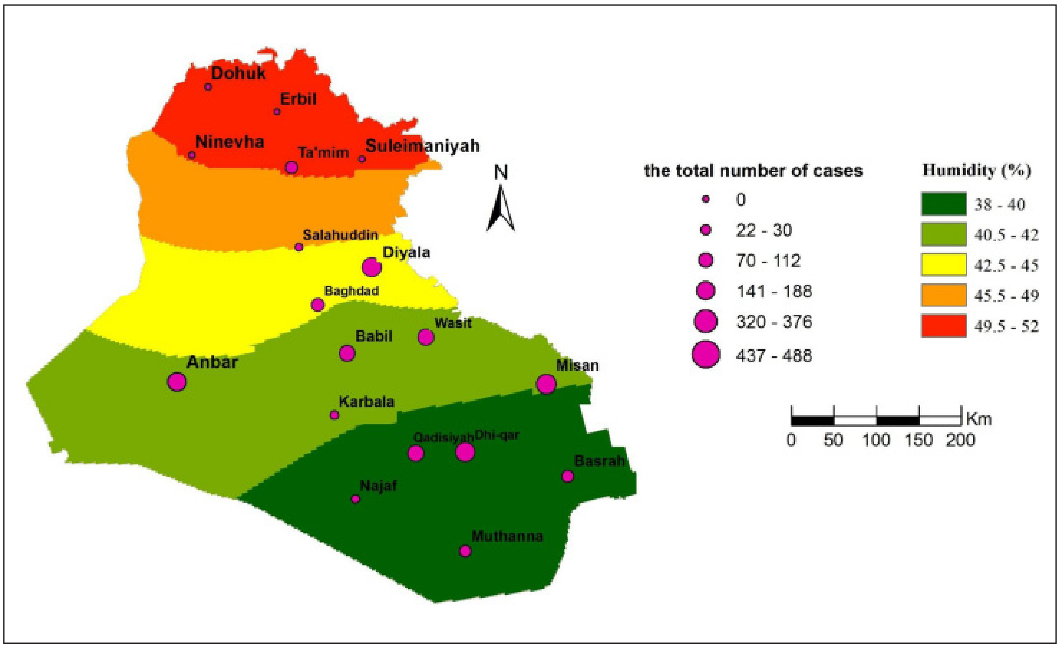

Figure 4d. Reported cases of kala-azar overlaid on an annual humidity map of Iraqi provinces.

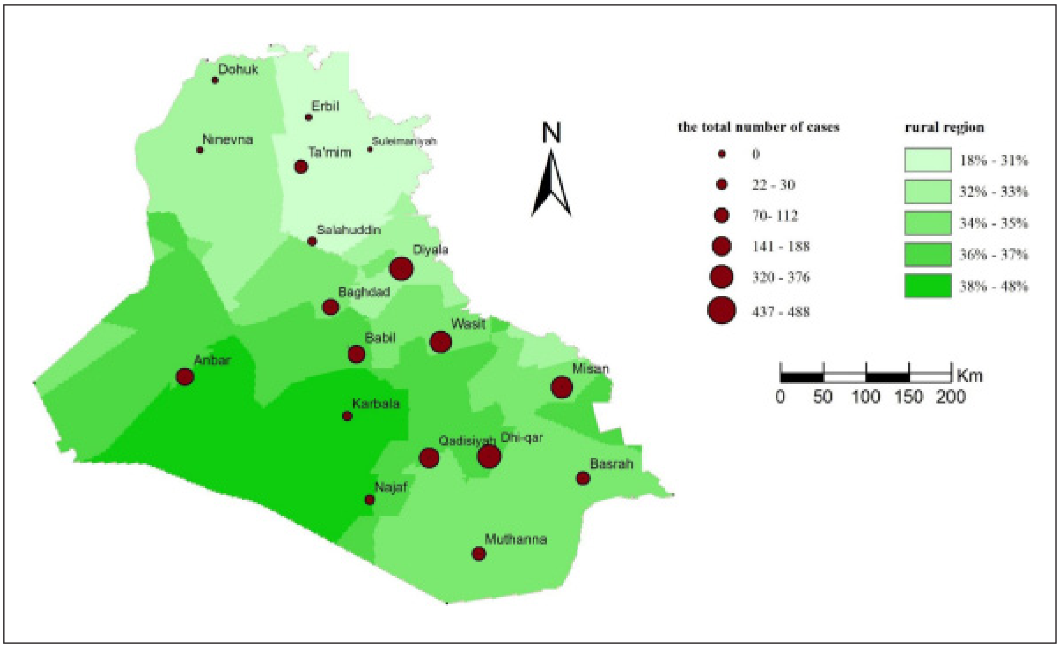

Figure 4e. Distribution of the percentage of rural people inhabiting Iraqi provinces, overlaid with data on the number of kala-azar cases.

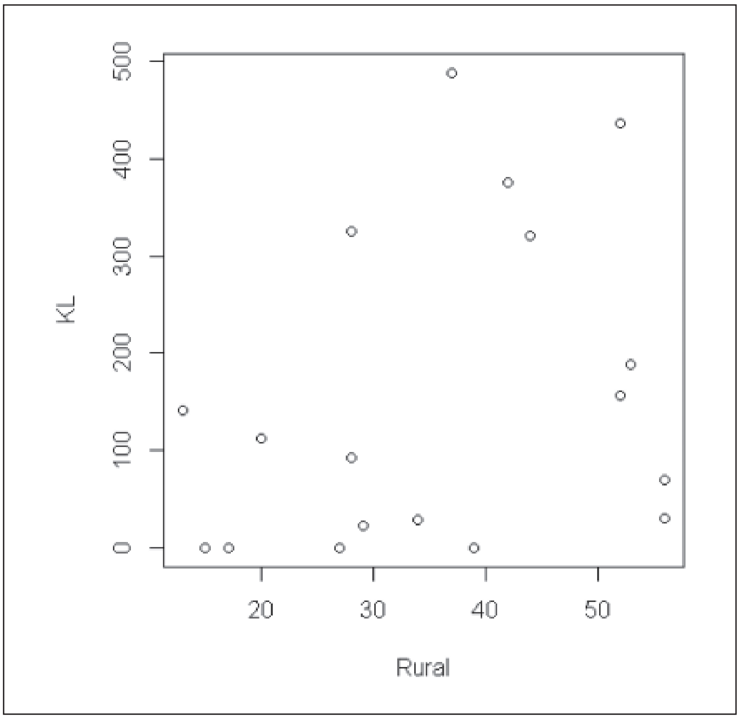

Figure 4f. Association between kala-azar cases (KL) and the percent of the province's population that is rural; F=1.656; P=0.2165.

Most of the provinces along the Iraq–Iran border had high numbers of kala-azar cases. In addition to the socio-cultural and socio-economic similarity, open borders between these provinces and the western regions of Iran facilitate cross-border trade and population movements, which may also play a critical role in the maintenance and spread of kala-azar. Ebrahimi *et al.* (2016) note that indigenous and traveler populations in these regions are at risk in these cross-border areas. Furthermore, the similar zoogeography of Iraq and Iran suggest a sharing of reservoir and vector species for the pathogens (Al-Sheikhly *et al.*, 2015), and cross-border *Leishmania* infections have been recorded in previous studies (Rowland *et al.*, 1999; Pandey *et al.*, 2009; Alawieh *et al.*, 2014).

Our descriptive results also suggest that the regions lacking confirmed kala-azar cases have higher elevations and colder weather. This finding is consistent with results reported by Costa *et al.* (2009) who showed that leishmaniasis was not normally found at high-elevation because of decreases in sandfly density. In contrast, we did not observe strong correlations between kala-azar incidence and the annual means of rainfall or humidity. Such patterns have been reported elsewhere, with high case numbers seen in areas of low and moderate annual rainfalls. These patterns can be correlated with the distribution or the high density of particular species of sandfly vectors such as *P. papatasi*, which have been recorded in some of these provinces (Al-Azawi & Abul-Hab, 1977). Thus while the broad patterns observed in this study are informative, the preferences that particular species such as *P. papatasi* show for habitats with moderate rainfall and humidity (Srinivasan *et al.*, 1993; Signorini *et al.*, 2014; Ebrahimi *et al.*, 2016) suggest that finer-scale spatial analyses of kala-azar occurrence may further refine our understanding of the persistence of the disease. Nonetheless, our findings may provide some guidelines for investigators assessing management approaches for the control of kala-azar in Iraq.

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