

**Distribution pattern of anthroponotic cutaneous leishmaniasis caused by
Leishmania tropica in Western Afghanistan during 2013-2014**

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Abstract

Anthroponotic cutaneous leishmaniasis (ACL), caused by *Leishmania tropica*, is the main cause of cutaneous leishmaniasis (CL) in the Herat province, Western Afghanistan. We investigated the role of environmental factors on ACL distribution in Herat. Epidemiological data from 2457 patients were retrieved from the local WHO sub-office. Shapefile layers of districts, cities, villages, land cover, soil type and digital elevation model (DEM) of the Herat province were used to assess, by logistic regression modelling, the effects of land cover, soil types, elevation, and proximity to the Harirud river on the distribution of ACL.

The key determinants of distribution were: (i) close proximity to the Harirud river, (ii) elevation between 700–1200 m, (iii) intensive and intermittent irrigated cultivated land, and (iv) Haplocalcids with Torriorthents and Torrifluvents soil types. No ACL cases were found below 700 m, and a few cases were present at > 1200 m in irrigated areas around the Harirud river. These findings suggest that moist soil and the humidity from irrigated areas found between 700-1200 m provide suitable breeding sites of *Phlebotomus sergenti*, the main sandfly vector of *L. tropica* in Afghanistan. The effect of elevation also explains the predominance of ACL over ZCL in this region. The present study showed that distribution of ACL is strongly associated with environmental factors in West Afghanistan where the political and socio-economic conditions may also affect the epidemiology of CL.

Key words: Afghanistan; Anthroponotic Cutaneous Leishmaniasis (ACL); GIS; Epidemiology; Environmental factors

1. Introduction

Leishmaniasis is a vector-borne neglected parasitic disease, with a wide spectrum of manifestations caused by the *Leishmania* spp., which is transmitted by sandflies. Cutaneous

leishmaniasis (CL) is the most common form of disease. Anthroponotic cutaneous leishmaniasis (ACL) and zoonotic cutaneous leishmaniasis (ZCL) are the most common types of dermal leishmaniasis. Worldwide, the annual incidence of CL is estimated at 0.7 to 1.2 million cases in 82 countries, with 70-75% of cases occurring in 10 countries, including; Afghanistan, Syria, Iran, North Sudan, Algeria, Ethiopia, Brazil, Peru, Colombia and Costa Rica (Alvar et al., 2012). CL remains a major public health problem in 14 of the 22 countries of the Eastern Mediterranean Region (EMR) of the World Health Organization (WHO), especially Afghanistan (Postigo, 2010). The true burden of CL is largely unknown, partly because the most affected people live in remote areas with no access to treatment (Alvar et al., 2012).

CL in Afghanistan is either ZCL, due to *Leishmania major*, or ACL due to *Leishmania tropica*. *L. tropica* accounts for most of the CL burden, and there has been a prolonged epidemic of ACL in eastern Afghanistan since 1987 (Faulde et al., 2006). Humans are the main reservoir of *L. tropica*, and the great gerbil *Rhombomys opimus* is the principal reservoir of *L. major*; the rodent *Meriones libycus* is of secondary importance (Faulde et al., 2008b, Nadim et al., 1979a). *Phlebotomus sergenti* and *P. papatasi* are the main sandfly vectors for ACL and ZCL, respectively (Killick-Kendrick, 1999).

The current ACL epidemic in Afghanistan is due to several factors, including a breakdown of vector control, the destruction of the public health infrastructure, resulting in poor access to treatment, and internal displacement of people from non- to endemic areas in consequence to decades of war (Reithinger et al., 2003). The main endemic foci of CL include the provinces of Kabul, Parwan (no data on CL type), Kandahar, Kunduz, Balkh, Badakhshan, and Herat (Plourde et al., 2012; Faulde et al., 2008a,b; Nadim et al., 1979a,b; Nadim and Rostami., 1974; Reithinger et al., 2003). ACL predominates in most provinces except for Kunduz and Balkh (**Fig. 1**). Endemic foci of CL in Western Afghanistan are distributed in different parts of the Herat province (Nadim et al., 1979b), where the incidence of ACL has increased in some districts in recent years (Fakhar et al., 2016). The province is surrounded by some well-established and newly defined foci of ACL in Afghanistan, including Kabul in eastern and Kandahar in southeastern Herat, and in Iran, such as Mashhad in northwest, Birjand in west and Bam and Kerman (and also Shiraz, the more distant focus) in southwest of Herat

(Plourde et al., 2012; Reithinger et al., 2003; Nadim et al., 1979b; Izadi et al., 2016; Ghatee et al., 2013; Ghatee et al., 2014; Karamian et al., 2016).

The identification of CL in Afghanistan is been based on clinical criteria and the microscopic detection of *Leishman* bodies (amastigotes) on a Giemsa stained slide; a limited number of studies have used molecular methods to identify the species from Mazar-e Sharif (Balkh province) and various locations in Herat and Kandahar (Faulde et al., 2008b ; Plourde et al., 2012. Fakhar et al., 2016).

The epidemiology and war associated risk factors of CL in Afghanistan have been characterized previously (Faulde et al., 2008a) but the role of climatic and environmental factors have not been studied. Geographical information systems (GIS) are valuable tools for studying the environmental and climatic factors and modelling the control of vector-borne diseases over time (Hongoh et al., 2011). We recently studied the epidemiology of CL in patients in Herat province and found that *L. tropica* was responsible for 98% of the CL burden (Fakhar et al., 2016). In the present study, we report on the role of environmental factors in the distribution of ACL in the Herat province using GIS.

2. Materials and methods

2.1. Study area

Located in the mountainous area of Central Asia, Afghanistan has a surface area of approximately 653'000 km², and a population of ~26.5 million. Afghanistan has been involved in a destructive war since the late 1970s and this has led to the destruction of the infrastructure and to large population movements within the country and across international borders. The main economic activity is agriculture, based more on man-power than mechanization.

The Herat province has a population of 1'852'800. It is an agriculturally rich province producing wheat, rice, grapes, apples, apricots and etc. The water source for cultivation is the Harirud river which arises in Central Afghanistan, crosses the Herat province and moves to the west and northwest, running parallel to the Afghanistan Iran border.

2.2. Collecting data on CL

CL data were collected from the Leishmaniasis Referral Laboratory in Herat city, a referral centre for the diagnosis and treatment of CL, which is administered by the Herat WHO Sub-office; it has a broad catchment area, seeing patients from across the Herat province. A unique feature of this centre is its ability to collect valid data despite years of war. From 2013 – 14, there were 3861 CL patients. We collected data using a standard case report form, including, age sex, lesion type, number and location of CL lesions and residential addresses. Some addresses were too imprecise to plot on the map and finally 2457 out of 3861 cases were included in the study.

2.3. Geospatial data

Shapefile map layers of Afghanistan, including villages, towns, cities, provinces, counties and country boundaries, were downloaded from Mapcruzin ([www. mapcruzin.com](http://www.mapcruzin.com)). Shapefile layers of land cover, soil types and raster layer of the digital elevation model (DEM) were also retrieved from <http://www.nrcs.usda.gov> and <http://spatialnews.geocomm.com>. ArcGIS 9.3 software (<http://www.esri.com/arcgis>) was used for geospatial analysis.

The Herat province land cover, soil types and DEM layers were clipped and extracted from the above-mentioned layers, and patients' residences at the village/town/city level were plotted ('infection points') on the shapefile point layer of the Herat province. The shapefile point layer of Herat province was extracted by DEM, and the obtained layer was computed by landcover and soil type maps to yield the final layer, which showed the properties of all of overlapping features from the raster and vector layers. The attribute of this layer was then converted to an excel format for statistical analysis. Using the ArcGIS 9.3 software, summary attributes were generated to study the frequency of infected points in each feature. A 12 km buffer zone around the Harirud river was generated to assess the role of proximity to the river on the distribution of ACL.

2.4. Statistical analysis

A binary logistic regression model was used for the analysis of the role of environmental factors on the occurrence of ACL. The model was optimized by reducing the categories of dependent variables, and finally four categories and five groups were regenerated for the landcovers and soil types variables, respectively.

Landcovers were categorized as rangelands and rocky/bare soils land, dry-fed farms, intensive irrigated areas and intermittently irrigated areas. Soil type groups included Haplocalcids with Torriorthents and Torrifluvents soils (group 1), Haplocambids with Torripsamments soil (group 2), Torriorthents with Torrifluvents (group 3), Torrifluvents with Torripsamments (group 4), and different rocky lands, salt flats, Xerorthents with Xeropsamments and Haplosalids soil types (group 5). Group 5 made up the reference soil group for analysis in the model. Elevation was categorized in three levels: 0-700, 701-1200 and > 1200 metres (m) regarding distribution of infected points on the DEM map. In the binary logistic regression model, > 1200 m category was the reference elevation. Chi-square analysis was used for the evaluation of effect of living within the 12 km river buffer zone on the occurrence of ACL.

3. Results

3.1. Demographic and epidemiological data

Of the 3861 patient records, 2457 (63.3%) subjects were included in this study. 51.3% of the subjects were males and 48.7% were females. Ages ranged from < 1 year to 94 years, for a mean of 15.97 y. Acute form of the disease was found in 2079/2457 (84.6%) of patients, while 292/2457 (11.9%) were registered as chronic, and only 3.5% of patients were classed as recurrent leishmaniasis. The lesions were mainly found on the face and neck (63%); other locations were the upper (25.5%) and lower limbs (10.9%) and trunk (1.6%). The majority of patients 1713/2457 (69.7%) had one lesion, 511/2457 (20.8%) had two, 147/2457(6%) had three and 86/2457 (3.5%) had 4 or more lesions. The highest number of lesions seen was 11.

The clinical forms of the disease were: (i) nodules (1302, 53%), (ii) ulcers (725, 29.5%), (iii) papules (327, 13.3%), and (iv) lupoid (103, 4.2%) forms. The 2457 CL cases came from 187 villages, towns, and cities. Lupoid cases were reported in 21 points (20 were found around the Harirud river); other clinical forms were found in different regions.

3.2. Infected points and the Harirud river risk zone

Most CL cases in the Herat province were located around the Harirud river: 137 (73.2%) of 187 points were distributed within the 12 km buffer zone. Close proximity to the Harirud river was considered as a risk factor ($P < 0.01$), although no cases were reported in the east regions of this buffer (**Fig. 2A**).

3.3. Infected points and land elevation

Elevation was a significant explanatory variable, with an OR (odds ratio) of 5.32 (95% CI 3.49-8.13 $p < 0.001$) for the category of 700-1200 m elevation (vs. the > 1200 m reference). Most of the infection points (160 /187) were found in this area. No infection points were located < 700 m, while 27 infected points were reported in the elevation above 1200 m. Patients were found in an altitude range of 719 to 2046 m (**Fig. 2B**).

3.4. Infected points and land cover

Most areas in the Herat province are covered by rangeland and rocky outcrop with bare soil. Rain-fed areas and irrigated lands were in the next ranks, respectively (**Fig. 3A**). Intensive and intermittently irrigated areas were the landcovers associated most significantly with CL with respective ORs of 14.34 (95% CI 8.04–26.16, $p < 0.001$) and 13.15 (95% CI 6.59–26.29, $p < 0.001$). Rocky/bare soil lands also were considered as the effective landcover on the occurrence of CL in this province (OR= 9.53 95%CI 4.98-18.21 $p < 0.001$). The least cases were reported from rangelands and dry-fed farms (rain-fed crops).

3.5. Infected points and soil types

Of the different soil types in the Herat province (**Fig. 3B**), Haplocalcids with Torriorthents and Torrifluvents soils were associated with 155 (82.8%) of 187 infected points and had the highest CL association: OR=13.08 (95%CI 6.98-24.51, $p < 0.001$). The impact of Haplocambids with Torripsamments soil types was notably less compared to group 1 soil types. Groups 3 and 4 showed no effect on the occurrence of CL in this region (**Table 1**).

4. Discussion

Our study has shown that most of infected points were clustered within the 12 km hazard map around the Harirud river. This close proximity as well as landcover, soil type and elevation

were important factors explaining the distribution of CL cases in the Herat province. Although irrigated farms cover only small parts of the Herat province, most of the infected points were distributed in these areas. The rocky/bare soil lands were associated with ACL (albeit at a lower risk), but the landcover map analysis showed that most of infected points in these areas were distributed close to micro irrigation areas. These farmlands are irrigated by the channels from the main branch of the Harirud river and other smaller rivers and are concentrated around the Harirud. In central Algeria, Garni *et al.* (2014) showed the importance of a combination of close proximity to the Mزاب river, palm groves, and irrigated grounds near settlements on the occurrence of ZCL caused by *L. Major*, as well as the presence of *P. papatasi* and rodents.

Villages, towns and cities with ACL cases were distributed mostly in the intensive and intermittent irrigated regions, where the land is moist and vegetation cover abundant; these environmental conditions favour the successful breeding of *P. sergenti*, the vector responsible for transmitting *L. tropica*. Some studies have shown the negative effect of aridity in comparison to humid grounds on the incidence of both *P. papatasi* and *P. sergenti* (Müller et al., 2011; Boussaa et al., 2016).

The distribution of the infected points within the 12 km risk zone was not uniform. Most cases were found in the central and western regions of risk zone in Injil, Guzara and Goryan districts, while no infected points were found in Obe and Shistisharif in the eastern regions. The Harirud river originates in the Baba mountains of the Hindu Kush in Central Afghanistan and runs downstream from east to west. The DEM map showed a decrease in elevation from east to west, and no cases occurred > 1200 m elevation in the risk zone, but 27 infected villages were found above 1200 m outside of the zone. Therefore, elevation above 1200 m limits the occurrence of ACL, and this may be related to an environment (e.g. cooler temperatures) that inhibits the breeding of *P. sergenti* and reduces its survival. Elevation is also a limiting factor for the occurrence of the visceral leishmaniasis in the Middle East and the Mediterranean basin (Ghatee et al., 2013; Elnaiem et al., 2003; Pérez-Cutillas et al., 2015). Our results show that ACL infected points were most common at elevations 700–1200 m in West Afghanistan, and are consistent with one study from Morocco, which showed that an elevation range of 800–1200 m was optimal for the presence of *P. sergenti*; > 90% of

the sergenti sand fly population was found within this range (Guernaoui et al., 2006). The effect of elevation also explains the lack of ZCL in Herat, consistent with other works that report that *P. papatasi* transmitted *L. major* occurs mostly in the lowlands, usually below 600-700 m (Guernaoui et al., 2006; Mollalo et al., 2015; Samy et al., 2016).

Of the 187 infection points, 155 points were found in Haplocalcids with Torriorthents and Torrifluvents soil types. Haplocalcids soil type is usually associated with a mean annual rainfall of ~200 mm and Torriorthents with aridic soil moisture that has a high salt concentration (Brungard, 2009). The Torrifluvents soil consist of alluvial soil and is found around rivers, adjoining flood zones, and irrigated crops in deserts. We hypothesize that Torrifluvents soil with sufficient humidity and alluvial debris, and also Haplocalcids with Torriorthents soil, which encompasses farmlands which are irrigated with water channels from the Harirud river, can provide suitable breeding places for *P. sergenti*. This notion is supported by work showing that soils that retain water and are used for cultivating crops promote sandfly breeding and activity in leishmaniasis endemic foci (Sudhakar et al., 2006; Ranganathan et al., 2015). Palaniyandi et al. (2014) showed that *P. papatasi* and *P. orientalis* are prevalent in humid alluvial and black cotton soils in India and, in another Indian study, Kesari et al. (2011) demonstrated a high incidence of *P. argentipes* in high moisture alluvial soil.

Haplocambids with Torripsamments soil was also associated with CL, but had a weaker association compared to Haplocalcids with Torriorthents and Torrifluvents soil types. Haplocambids soil is found mostly at high altitudes with cooler climates and Psamment soil also has a low water capacity. The close proximity of these infected points to the high risk land covers (irrigated areas) and soils (humid Haplocalcids with Torriorthents and Torrifluvents soils), suggests a role for human movement from high risk regions to neighbouring villages e.g. farm workers working in the irrigated farms.

Our previous molecular based study from the Herat province showed that the almost all studied CL cases (125/127) were ACL caused by *L. tropica*, distributed chiefly around the Harirud river as well as in more distant points to the north and southwest of the river (Fakhar et al., 2016). *L. major* was found in two points, Shewan village, in the heart of the risk zone

(Injil district) by the Harirud river, and Sangbur village, in the south of province and far from the Harirud in Shindand district. Shewan is a village in the irrigated area with Torrifluvents soil at 919 m elevation, all factors favouring ACL. Sangbur, at 1209 m elevation, is also in an irrigated area but the soil type is Haplocambids with Torripsamments. These ZCL patients may be isolated imported cases, given the unfavourably high elevation for papatasi sandfly breeding. Many years of war have brought about the mass movement of people in Afghanistan from endemic and non-endemic CL areas, and this could explain partly the high ACL endemicity around the Harirud river and the few cases of ZCL (there are no data on population movements for the Herat province). Population displacement is a classic risk factor for the rise of CL in Afghanistan (Reithinger et al., 2003; Reyburn et al., 2003).

In the Herat province, two different *L. tropica* populations exist, based on the sequence analysis of the internal transcribed spacer 1 (ITS1) of ribosomal DNA (Fakhar et al., 2016). The predominant population consists of ITS1 sequence types (ST) 1 and 2, and the minor population of ST3 and 4 isolates, but these two populations were found in essentially the same soil types, landcovers and elevations (**Table 2**). The *L. tropica* ST3 and 4 subtypes originated from Southeast-East Iran (Karamian et al., 2016; Fakhar et al., 2016) where the environment, like in Western Afghanistan, is dry. The most prominent environmental difference between these regions and eastern Herat is the Harirud river and the extensive irrigation system it feeds. Therefore, finding ST3 and 4 subtypes mixed with ST1 and 2 subtypes in the 12 km zone suggests ST3 and 4 adaption to the humid environment of Herat, probably by the adaption of the *P. sergenti* sandfly. There are no phylogenetic genetic data on *P. sergenti* and very limited data on *L. tropica* in Afghanistan, so the notion of environmental adaption is speculative. Climatic changes affect bioclimatic zones (Ready, 2010). Southeast and East Iran have been affected by drought lasting for decades that has reduced drastically these regions' major rivers (e.g. Dehbakri and Nesa in the Southeast, and Shahrood in the East of Iran), which were considered as important sources of water in previous century. Similarly, the lack of ST1 and 2 subtypes in southeast and eastern Iran suggests a role of environmental factors on the distribution of *Leishmania* strains in these regions.

5. Conclusions

Key environmental factors associated with distribution of ACL in West Afghanistan are the Harirud river, farm irrigation, Haplocalcids with Torriorthents and Torrifluvents soils types and an elevation range of 700-1200 m; these may provide suitable humidity and temperatures to support the breeding and survival of the *P. sergenti* sandfly. The elevation factor also explains the predominance of ACL over ZCL in the Herat province. Differences between Herat and neighboring regions in Iran in *L. tropica* populations suggest adaptation from arid regions of Southeast-East Iran to humid conditions around the Harirud river. Lack of data preclude conclusions regarding the role of population movement into the Herat province. More data are needed to track the burden of CL as the climate changes and strategies explored on how to reduce the vector population and protect those at risk, mostly farm workers.

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