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Modeling the Distribution of Cutaneous Leishmaniasis Vectors (Psychodidae: Phlebotominae) in Iran: A Potential Transmission in Disease Prone Areas

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ABSTRACT Cutaneous leishmaniasis (CL) is now the main vector-borne disease in Iran. Two forms of the disease exist in the country, transmitted by *Phlebotomus papatasi* and *Phlebotomus sergenti* s.l. Modeling distribution of the vector species is beneficial for preparedness and planning to interrupt the transmission cycle. Data on sand fly distribution during 1990–2013 were used to predict the niche suitability. MaxEnt algorithm model was used for prediction using bioclimatic and environmental variables (precipitation, temperature, altitude, slope, and aspect). Regularized training, area under the curve, and unregularized training gains were 0.916, 0.915, and 1.503, respectively, for *Ph. papatasi*. These values were calculated as 0.987, 0.923, and 1.588 for *Ph. sergenti* s.l. The jackknife test showed that the environmental variable with the highest gain when used in isolation has the mean temperature of the wettest quarter for both species, while slope decreases the gain the most when it is omitted from the model. Classification of probability of presence for two studied species was performed on five classes using equal intervals in ArcGIS. More than 60% probability of presence was considered as areas with high potential of CL transmission. These areas include arid and semiarid climates, mainly located in central part of the country. Mean of altitude, annual precipitation, and temperature in these areas were calculated 990 and 1,235 m, 273 and 226 mm, and 17.5 and 16.4°C for *Ph. papatasi* and *Ph. sergenti* s.l., respectively. These findings can be used in the prediction of CL transmission potential, as well as for planning the disease control interventions.

KEY WORDS cutaneous leishmaniasis, *Phlebotomus papatasi*, *Phlebotomus sergenti* s.l., niche modeling, Iran

Cutaneous leishmaniasis (CL) is the main vector-borne disease in Iran, with ~20,000 cases reported annually (Yaghoobi-Ershadi 2012). Two types of CL exist in Iran, i.e., zoonotic cutaneous leishmaniasis (ZCL) and anthroponotic cutaneous leishmaniasis (ACL). Although in recording and reporting of CL cases, it is not common to do polymerase chain reaction (PCR) tests to detect the type of disease, the lesion morphology is considered as differential diagnosis, so that wet and dry lesions are used to describe ZCL and ACL, respectively. By the way, research studies in different foci were conducted to detect the parasite species. For this reason, data on CL incidence in the country are not divided into ACL and ZCL. Based on the published data, Fars and Ilam provinces had the most incidence of CL

in the past decade, followed by Esfahan, Kerman, Yazd, Bushehr, Khorassan-e-Razavi, Semnan, and Kohgiluyeh va Boyer-Ahmad (Karimi et al. 2014).

The main form of CL in Iran is ZCL. It has endemic foci in rural areas of 17 of 31 provinces of the country (Yaghoobi-Ershadi 2012). Main foci for ZCL are located in central (Esfahan, Qom, Yazd, Semnan, and Kerman provinces), northeast (Khorassan-e-Shomali and Golestan provinces), southeast (Baluchestan area), south and southwest (Fars, Ilam, Bushehr, Khuzestan, and Hormozgan provinces) parts of the country (Nadim et al. 2009). *Phlebotomus papatasi* was reported to be the main vector of this form of the disease in the mentioned foci, although *Phlebotomus salehi* is considered as the secondary vector in Baluchestan and Fars provinces, where *L. major* was detected by molecular methods (Yaghoobi-Ershadi and Javadian 1996; Yaghoobi-Ershadi and Akhavan 1999; Kasiri and Javadian 2000; Yaghoobi-Ershadi et al. 2001, 2005; Rassi et al. 2008; Nadim et al. 2009; Parvizi et al. 2010; Davami et al. 2011; Azizi et al. 2012). *L. major*, the causative agent of ZCL in Iran, was also isolated or detected in some endemic areas of the disease in the

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country from the *Phlebotomus caucasicus* group and *Phlebotomus ansarii* as well, but these two species circulate the parasite among reservoir rodents (Yaghoobi-Ershadi and Javadian 1997, Yaghoobi-Ershadi 2012). As *Ph. caucasicus* showed to have 20% tendency to human blood, it is also considered as secondary vector of ZCL (Yaghoobi-Ershadi 2012). A review on the spatial distribution of *Ph. papatasi*, the main vector of ZCL, showed that it is a commonly reported species in almost all entomological surveys on sand flies of Iran (Karimi et al. 2014).

Regarding ACL, it was reported in 8 of the 31 provinces. The main foci were reported in large- and medium-sized cities such as Kerman, Bam, Yazd, Mashhad, Shiraz, and some parts of Esfahan (Nadim et al. 2009). It was also common in northern parts of Tehran in the past; some of these areas are not yet infected. ACL has longer duration of lesion than ZCL, human is the main reservoir host for this form, and it occurs in both endemic and epidemic forms in Iran (Nadim et al. 2009). *Phlebotomus sergenti* s.l. was known to be the main vector of ACL in Iran and was reported in 26 provinces of the country (Karimi et al. 2014). The density of this sand fly in human dwellings of the endemic foci of ACL is high, while in other parts, it can be found in foothills and mountainous areas with higher densities than plains and lowlands (Nadim et al. 2009). Promastigote infection was found in *Ph. sergenti* s.l. in some foci (Mesghali et al. 1967) and *L. tropica* was detected by the PCR method from this sand fly (Oshaghi et al. 2010, Aghaei Afshar et al. 2014). *Ph. sergenti* s.l. has two forms including *Ph. sergenti sergenti* and *Ph. sergenti similis* in the country based on morphometrics and molecular studies. This sand fly is more or less distributed in different provinces of Iran (Moin-Vaziri et al. 2007).

Major risk factors for increasing the risk of CL are socioeconomic conditions, population mobility, environmental changes, and climate changes (WHO 2015). All of these factors are operational in Iran, so that dramatically urbanization trend during the past decades (United Nations 2014) sometimes resulted in crowded population in suburbs and outbreaks of CL. Recent climatic and environmental changes in the world is another risk factor for emerging CL in new areas owing to the expanding distribution of vectors or reservoirs of the disease. In other words, the establishment of non-native species in new geographical areas is possible due to their ability to adapt to climate change and new habitat conditions (Melaun et al. 2015). This scenario is studied in Middle East countries (Cross et al. 1996). So, risk assessment of vector-borne diseases is necessary to improve the health quality of the community.

Given the importance of CL in Iran, the objectives of this study are to model the best ecological niches of *Ph. papatasi* and *Ph. sergenti* s.l. as the main vectors of CL in Iran, to find the probable distribution areas for these sand flies species, and to stratify the country based on the chances of presence of CL vectors and, therefore, risks of disease transmission.

Materials and Methods

Study Area. Iran with an area of 1,648,195 km², is located between latitudes of 25° 3' and 39° 47' North, and 44° 5' and 63° 18' East. The country is bordered on the north by Armenia, Azerbaijan, Caspian Sea, and Turkmenistan, on the east by Afghanistan and Pakistan, on the south by the Persian Gulf and the Gulf of Oman, on the west by Iraq and on the northwest by Turkey (Fig. 1). Iran's climate ranges from arid or semiarid, to subtropical along the Caspian coast and the northern forests. Annual precipitation is 680 mm in the eastern part of the plain and >1,700 mm in the western part. To the west, settlements in the Zagros basin experience lower temperatures, severe winters with <0 average daily temperatures and heavy snowfall. The eastern and central basins are arid, with <200 mm of rain, and have occasional deserts. Average summer temperatures exceed 38°C in this part. The coastal plains of the Persian Gulf and Gulf of Oman in southern Iran have mild winters, and very humid and hot summers. The annual precipitation ranges from 135 to 355 mm in these areas (Meteorological Organization of Iran).

Species Data. Data on spatial distribution of sand flies were obtained from the IrSandflyBase (Karimi et al. 2014). This database includes >200 references on the sand flies of Iran. One of the main criteria for inclusion in the IrSandflyBase was to enter information that was published by experts in the field of sand fly taxonomy. The sample points for modeling included most recent data from faunistic studies on sand flies conducted during 1990–2013. They were 187 and 136 sites for *Ph. papatasi* and *Ph. sergenti* s.l., respectively (Fig. 2).

Model Variables. Bioclimatic variables and altitude layers were obtained from the WorldClim-Global Climate database at the spatial resolution of ~1 km or 30 arc-s (<http://www.worldclim.org/current>). Aspect and slope layer were prepared in ArcGIS 9.3 by surface analysis of altitude layer with the same spatial scale. These variables were derived from the monthly temperature and rainfall values to generate more biologically meaningful variables. These are often used in ecological niche modeling. The bioclimatic variables represent annual trends, seasonality, and extremity or limitation of environmental factors (Table 1). Then, layers were changed to ASCII raster using the ArcMap 9.3 model builder format for the following analysis in the MaxEnt model.

Modeling Potential Occurrence of Sand Flies. MaxEnt software version 3.3.3 was used to predict the appropriate ecological niches for given species; i.e., *Ph. papatasi* and *Ph. sergenti* s.l. (Phillips et al. 2006). Random test percentage for both species was 20%, so that for *Ph. papatasi*, 150 presence records were used for training and 37 for testing. About 109 *Ph. sergenti* s.l. presence records were used for training and 27 for testing. Jackknife analysis in the MaxEnt software was used to evaluate the contribution of the environmental variables. All variables with no contribution (0 values) were excluded from the final analysis (Table 1). This table gives estimates of relative contributions of the environmental variables to the MaxEnt



Fig. 1. Map of Iran.

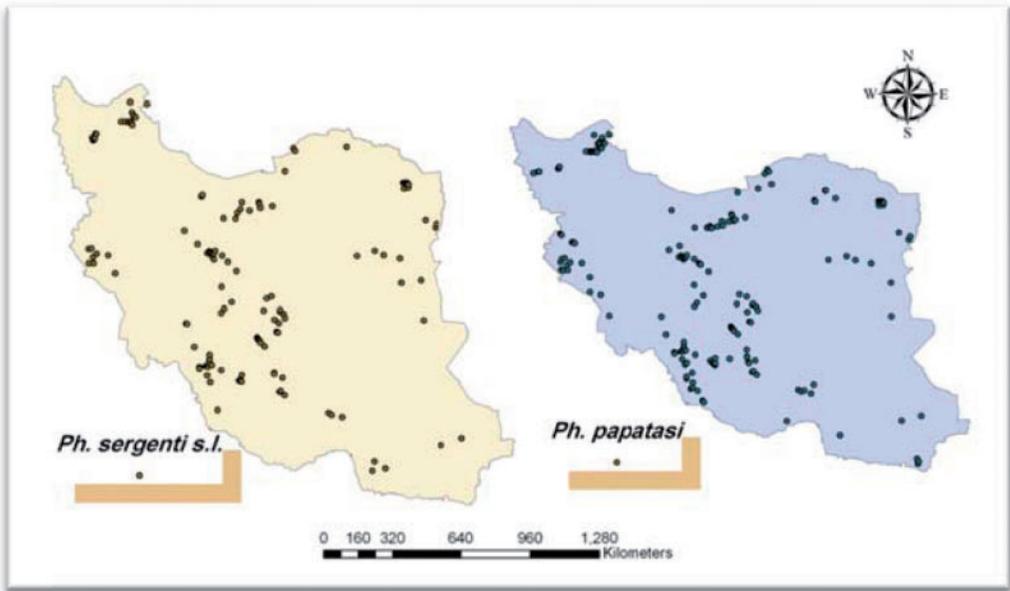


Fig. 2. Sampling sites of vectors of CL in Iran used for modeling from 1990 to 2013.

model for each species. To determine the first estimate in each iteration of the training algorithm, the increase in regularized gain was added to the contribution of the corresponding variable, or subtracted from it if the change to the absolute value of lambda is negative. For the second estimate, for each environmental variable, in turn, the values of that variable on training presence and background data were randomly permuted. The model was reevaluated on the permuted data, and the

resulting drop in training area under the curve (AUC) is shown in the table, normalized to percentages. As with the variable jackknife, variable contributions should be interpreted with caution when the predictor variables are correlated.

Stratification of CL Transmission-Prone Area. Final ASCII raster outputs due to the potential occurrence of both studied sand flies were used for classification of the vector presence in ArcMap. Five

Table 1. Variables used to predict the potential distribution of sand fly vectors of CL in Iran

Variable	Description	Contribution (%) for species	
		<i>Ph. papatasi</i>	<i>Ph. sergenti</i> s.l.
Alt	Altitude from the sea level (m)	2.8	5.1
Slope	Slope obtained from altitude	16.7	11.8
Aspect	Aspect of the slope obtained from altitude	0.4	0.3
BIO1	Annual mean temperature	2	6.5
BIO2	Mean diurnal range [mean of monthly (max temp – min. temp)]	1.4	0.9
BIO3	Isothermality (BIO2/BIO7) (*100)	9.4	14.3
BIO4	Temperature seasonality (standard deviation *100)	1.1	3
BIO5	Max temperature of warmest month	3.2	4
BIO6	Min. temperature of coldest month	6.8	1.4
BIO7	Temperature annual range (BIO5-BIO6)	2.1	5.4
BIO8	Mean temperature of wettest quarter	14.8	17.2
BIO9	Mean temperature of driest quarter	1.3	0.6
BIO10	Mean temperature of warmest quarter	0.2	0
BIO11	Mean temperature of coldest quarter	1.5	2.2
BIO12	Annual precipitation	10.7	6.3
BIO13	Precipitation of wettest month	5.5	0.1
BIO14	Precipitation of driest month	0	0.2
BIO15	Precipitation seasonality (coefficient of variation)	11	10.4
BIO16	Precipitation of wettest quarter	5.4	7.2
BIO17	Precipitation of driest quarter	1.8	0.8
BIO18	Precipitation of warmest quarter	1.7	0.5
BIO19	Precipitation of coldest quarter	0.2	1.9

classes were created using equal intervals of the software having 0–20, 21–40, 41–60, 61–80, and 81–100% probabilities of presence of the studied vectors. The past two classes, i.e., >60% probability of presence for each species were considered as areas with higher risk for CL transmission. These classes were then overlaid on altitude, annual mean temperature, and annual precipitation layers to find the ranges of the most important environmental variables in favorite ecological niches of each species in Iran.

Results

Maxent Model. *Phlebotomus papatasi.* Figure 3 shows a representation of the Maxent model for *Ph. papatasi*. Warmer colors show areas with better predicted conditions. They show the presence probability of this species that was calculated to be 0–0.97 and divided into five classes based on equal intervals of ArcMap (0–0.2, 0.21–0.4, 0.41–0.6, 0.61–0.8, and 0.81–0.97) within different provinces of Iran. So, this species seems to be distributed across the country. Considering >0.6 values as areas with the most

probability of presence for this sand fly, the range of favorable annual precipitation, mean annual temperature, and elevation were calculated in Table 2.

Phlebotomus sergenti s.l. A representation of the Maxent model for *Ph. sergenti* s.l. is shown in Figure 3. Warmer colors show areas with better predicted conditions. The presence and probability of this species in different provinces of Iran was calculated to be 0–0.96 and classified into five groups based on equal intervals of ArcMap (0–0.2, 0.21–0.4, 0.41–0.6, 0.61–0.8, and 0.81–0.96). This sand fly has more or less the same spatial distribution as *Ph. papatasi*. Considering >0.6 or 60% as areas with the most probability of presence for this sand fly, the range of favorable annual precipitation, mean annual temperature, and elevation was calculated and is presented in Table 2.

Analysis of Variable Contributions. As with the variable jackknife, variable contributions should be interpreted with caution when the predictor variables are correlated. Figure 4 shows the results of the jackknife test of variable importance. For both sand flies, the environmental variable with highest gain when used in isolation was Bio8, which therefore appears to have the most useful information by itself. Also, the environmental variable that decreased the gain the most when omitted was slope for the studied sand flies, which, therefore, appears to have the most information that is not present in the other variables. For *Ph. papatasi*, regularized training gain, training AUC, and unregularized training gain were 0.916, 0.915, and 1.503, respectively.

About *Ph. sergenti* s.l. regularized training gain, training AUC and unregularized training gain were 0.987, 0.923, and 1.588, respectively.

Considering the areas with high probability of presence for each species in CL transmission prone areas, Figure 5 was prepared in ArcMap and it can be used as hazard map for ZCL and ACL transmission in Iran. On the other hand, >18 provinces of Iran have areas with high potential for breeding both species. As shown in some provinces with high probability of presence for both species, there was no record for the studied sand flies. They are Kohgiluyeh va Buyerahmad, Hamedan, Markazi, Qazvin, and Lorestan provinces. Lack of data in these provinces was due to the lack of study in previous years, but in some areas, such as Lorestan and Kohgiluyeh va Buyerahmad provinces, there were reports of CL with low incidences (Fig. 6). Provinces with middle- to high incidence of CL are providing good ecological niches for both vectors.

Discussion

Number of training sample size in ecological niche model affects the quality of predictions of geographical distributions of a given species (Peterson et al. 2004). [Wisz et al. \(2008\)](#) stated that no algorithm can predict consistently well with sample size <30. In our study, >100 sample points were used to train the model for each species. Although evaluating the credibility and accuracy of the data reported in previous years is a controversial issue, this study used the most reliable data

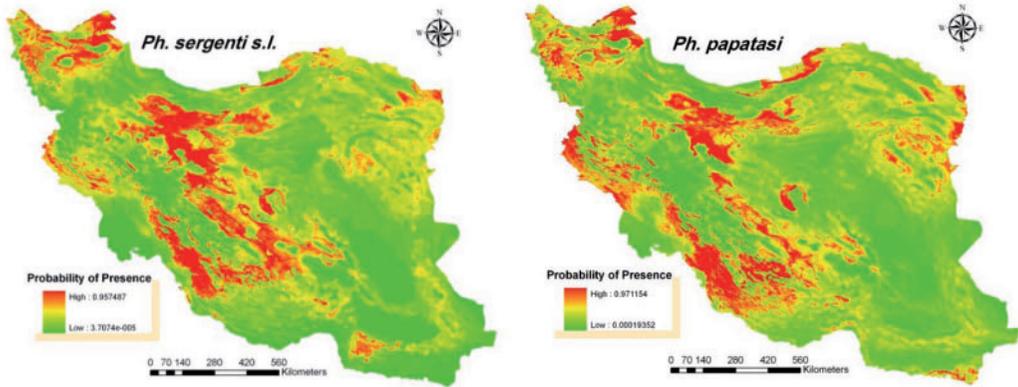


Fig. 3. Presence probability of *Ph. sergenti* s.l. and *Ph. papatasi* in Iran using the MaxEnt model.

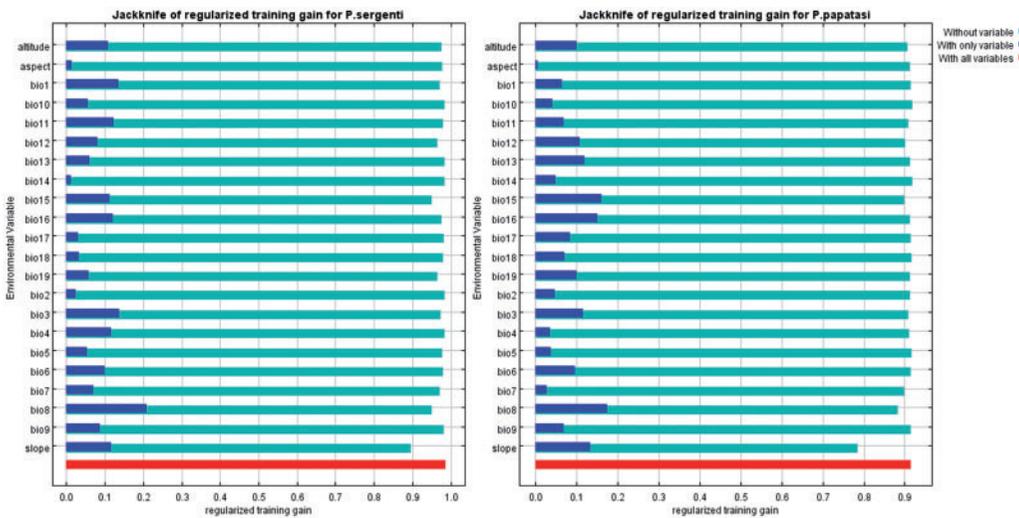


Fig. 4. Jackknife of regulated training gains for *Ph. sergenti* s.l. (left) and *Ph. papatasi* (right) in Iran.

for modeling. Owing to climate changes in the past few decades, modeling has been done based on the information in the past two decades. It is done primarily on the results of the studies of researchers at Department of Medical Entomology & Vector Control, School of Public Health, Tehran University of Medical Sciences, as the reference center for Medical Entomology in Iran. This will largely eliminate concerns about the validity of data. The pattern of vector distribution has been used for prediction of transmission risk of leishmaniasis (Elnaiem et al. 1998, Thomson et al. 1999, Gebre-Michael et al. 2004). Therefore, our study can be useful in prediction of vulnerability of different parts of Iran for CL transmission and its risk. On the other hand, the areas were modeled as suitable niches for each species, but until now, there is no report regarding this. Therefore, studies should be conducted because of the importance of this disease.

Several environmental factors were found to have affected the presence of sand flies in a given area. They include altitude (Ferreira et al. 2001, Simsek et al. 2007, Ozbel et al. 2011, Kassem et al. 2012), climate

Table 2. Statistics of three important variables in the areas with high probability of presence for CL vectors, Iran

Species	Variable	Min.	Max	Mean ± SD
<i>Ph. papatasi</i>	Altitude (m)	-24	2568	990 ± 471
	Annual precipitation (mm)	53	947	273 ± 128
	Annual mean temperature (°C)	3.6	26.5	17.5 ± 3.8
<i>Ph. sergenti</i> s.l.	Altitude (m)	-18	2236	1235 ± 532
	Annual precipitation (mm)	53	614	226 ± 109
	Annual mean temperature (°C)	7.5	24.2	16.4 ± 3.4

(Rispaïl et al. 2002), soil type (Elnaiem et al. 1998, Thomson et al. 1999), land cover (Colacicco-Mayhugh et al. 2010, Kesari et al. 2013), heat, humidity and availability of organic matter (Thomson et al. 1999, Naucke 2002, Ozbel et al. 2011, Kassem et al. 2012, Kesari et al. 2013), and precipitation (Quintana et al. 2013). Land cover was found to have had a strong contribution in distribution of sand flies, and the urban area

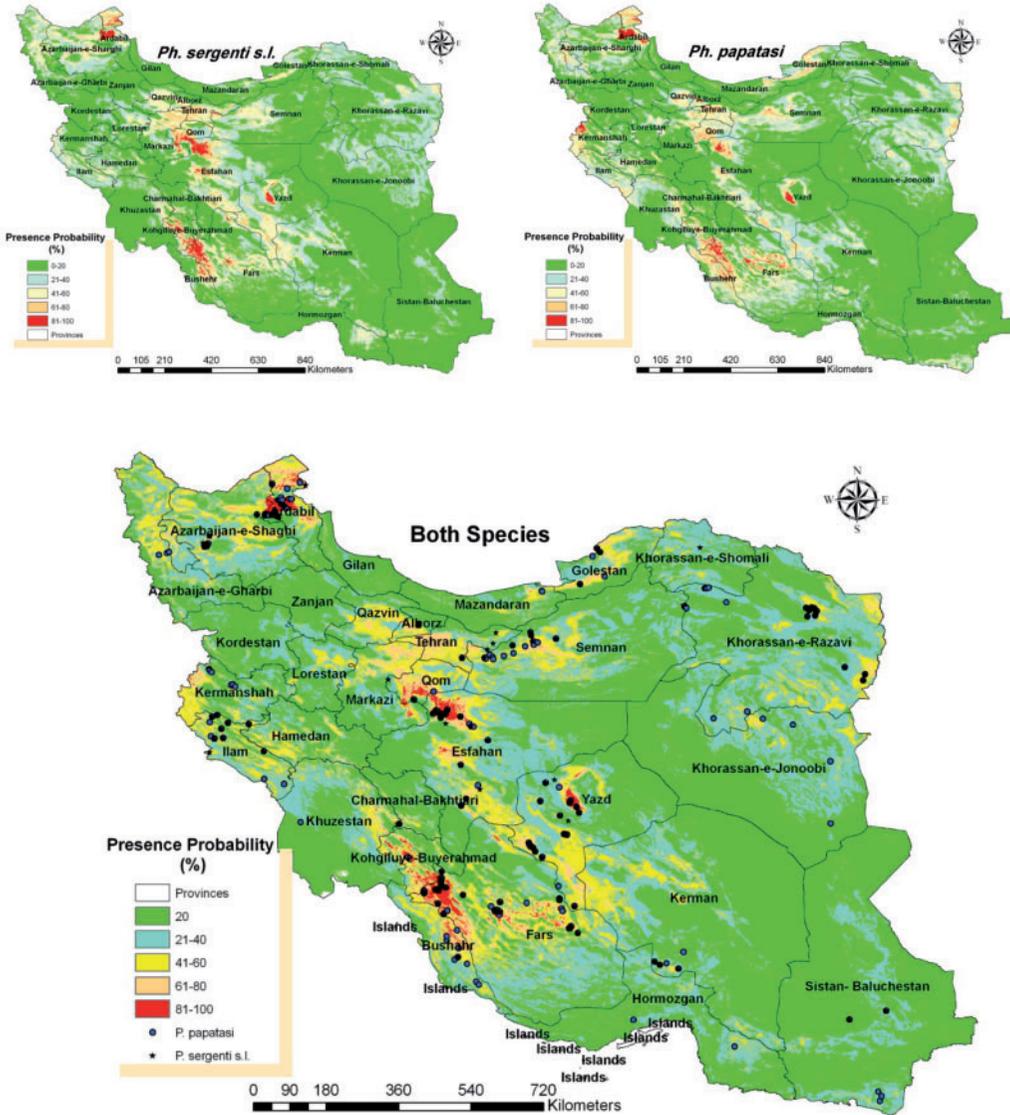


Fig. 5. Presence probability of main CL vectors in Iran.

was associated with high probability of these insects (Colacicco-Mayhugh et al. 2010). Mean monthly temperature range of 16–44°C was found to be favorable for *Ph. papatasi* (Cross et al. 1996). We found this range 3.6–26.5°C in the areas with >60% probability of presence for this sand fly. In Libya, high suitability for *Ph. papatasi* was predicted to be largely confined to the coast at altitudes <600 m. We found an average of 990 m for the altitude in the areas with >60% probability of presence for this species. Regions south of 30° N latitude were calculated as unsuitable for this species (Abdel-Dayem et al. 2012). In our study, slope, mean temperature of the wettest quarter, and precipitation seasonality had the most gains on prediction for this species (Table 1).

Ph. papatasi is a widespread species mainly in semi-arid and arid regions of the old world from Morocco to Indian subcontinent. They are proven vectors of CL in the old world (Maroli 2013). This species can be found everywhere in Iran with a high probability, as shown in Figure 5, and is a common and domestic sand fly in human and animal dwellings. The overall abundance of this species is higher in flat areas. Based on previous studies in Iran, it was collected from 7 to 2,240 m above sea level, while the model output showed a mean altitude of 990 m above the sea level in the areas with >60% probability of presence. It should be noted in mountainous areas, they can usually be found in human residential places with low densities. Although *Ph. papatasi* is an opportunistic species, it prefers the

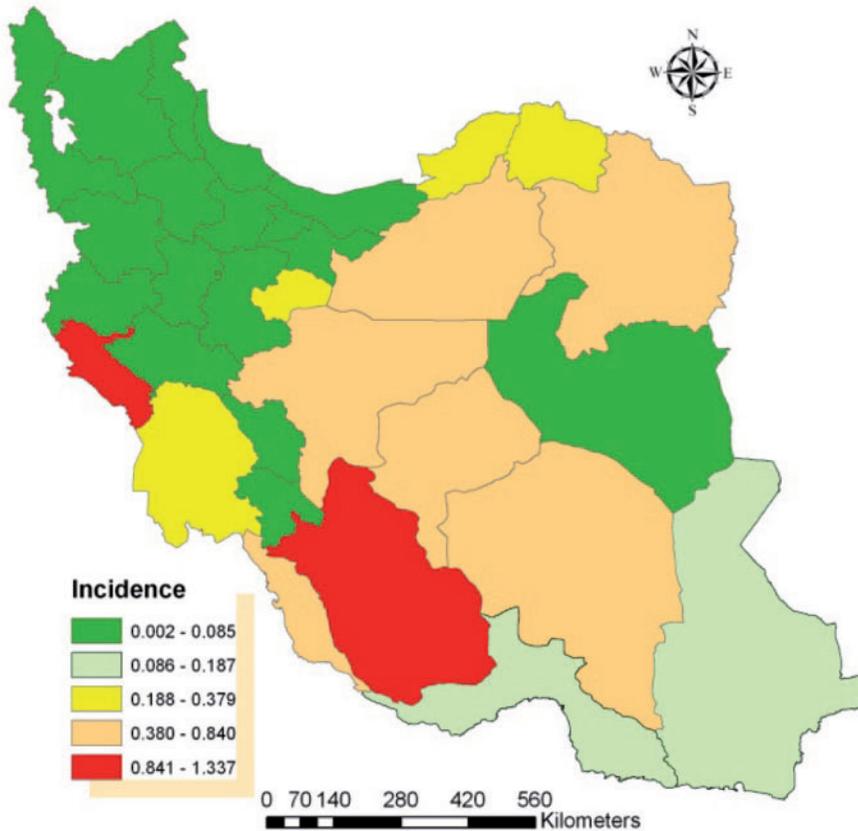


Fig. 6. Mean incidence of CL in difference provinces of Iran, 2003–2014.

human and rodent blood if available (Nadim et al. 2009, Yaghoobi-Ershadi 2012, Karimi et al. 2014). This sand fly was more abundant in the arid and Saharan bioclimatic zones of Tunisia and rare in the humid, sub-humid, and semiarid bioclimatic zones, where CL is endemic (Chelbi et al. 2009). In our study, we calculated means of annual temperature and annual precipitation as $17.5 \pm 3.8^\circ\text{C}$ and 273 ± 128 mm in the areas with $>60\%$ probability of presence for this species, respectively.

Ph. sergenti s.l. is a Mediterranean species that is distributed from south of Europe and north of Africa to north of the Indian subcontinent. In Iran, it has a high abundance in human residence of some cities. It is basically a mountainous species, with high tendency to the birds' blood (Nadim et al. 2009, Yaghoobi-Ershadi 2012, Karimi et al. 2014). Based on literature, it was collected from 40 to 2,232 m above sea level in Iran. Output of the MaxEnt model showed an average of 1,235 m for this species, ~ 250 m higher than *Ph. papatasi*. In other countries, it was reported from an ACL focus with an altitude of 2,000 m above sea level in Saudi Arabia (Al-Zahrani et al. 1988) and 1,600 m in Turkey (Simsek et al. 2007). Another study in Turkey showed *Ph. sergenti similis* had more density in an altitude of >500 m. General environment of the collection sites as well as DEM was found to be significantly

correlated with the abundance of this species (Ozbel et al. 2011). This species was reported to be a member of *Ph. sergenti* s.l. in Iran (Moin-Vaziri et al. 2007). Another study found *Ph. sergenti* has a tendency to congregate in rocky habitats with caves or boulder mounds. Collection of sand flies using emergence traps placed over bare soil, grass covered soil, dry river beds, valley slopes, rock covered soil, or dried sewage treatment basin had negative results (Moncaz et al. 2012). Mean annual temperature in the areas with $>60\%$ probability that this sand fly was present was $16.4 \pm 3.2^\circ\text{C}$, while mean annual precipitation for this class was found to be 226 ± 109 mm. Therefore, both species are mainly distributed in semi-arid areas, where CL foci of the country area.

Humans are one of the blood resources for sand flies, especially anthropophilic species. So these insects will drive to urban areas, where their hosts and plants (as sugar resources) are more readily available. However, the sampling bias toward areas with human leishmaniasis should be considered, if land use is one of the model inputs. Samples used in our study were collected mainly by sticky paper traps, although in some studies they have used CDC light traps. Sampling method is a critical factor affecting species composition of the sample (Alexander 2000, Hesam-Mohammadi et al. 2014). On the other hand, sampling place and method, as well

as vegetation, can affect the results of niche modeling. So, it should be noted that sampling methods as well as environmental layers used for modeling can introduce bias in the results.

In zoonotic CL foci, the main intervention strategy is control of reservoir hosts (gerbils) seconded by the distribution of long-lasting insecticide impregnated nets to the affected population. Indoor residual spraying was also carried out in the epidemic situations by the use of deltamethrin. Regarding anthroponotic CL, both indoor residual spraying and long-lasting insecticide impregnated nets were used in control programs. Study on the susceptibility level of CL vectors to insecticides in Iran showed susceptibility of both *Ph. papatasi* and *Ph. sergenti* s.l. to deltamethrin (Aghaei Afshar et al. 2011), which indicates the use of IRS intervention. Based on the results of this study, low endemic provinces with high probability of presence of one or both CL vectors should be considered as research priorities to prevent the probable epidemics in future.

The result of this study presents the first prediction on distribution of CL vectors in Iran. We found that climatology and topography variables such as precipitation, mean temperature, and slope had high contributions toward the prediction of potential distribution of both vector species. It is suggested that an improvement be made regarding the accuracy of the model via sand fly collection from the areas where it is predicted to have high presence of probability for each species. The models should be updated using periodical studies on sand flies in 5-yr intervals because of climate change.

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