International Journal of Infectious Diseases 90 (2020) 206–212

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Epidemiology and spatiotemporal analysis of visceral leishmaniasis in Palestine from 1990 to 2017

Ahmad Amro

Faculty of Pharmacy, Al-Quds University, Main Campus, P.O. Box 5100, Abu Dies, Jerusalem, Palestine

ARTICLE INFO

Article history:
Received 17 September 2019
Received in revised form 28 October 2019
Accepted 30 October 2019

Keywords:
Visceral leishmaniasis
Epidemiology
Spatiotemporal analysis
Leishmania infantum
West Bank
Palestine

ABSTRACT

Objectives: Visceral leishmaniasis (VL) is a deadly disease endemic in all countries around the Mediterranean Sea. In Palestine, VL is transmitted to humans from infected dogs by a sandfly bite. The aim of this study was to investigate the epidemiology and spatiotemporal pattern of VL in Palestine within a period of 27 years (1990–2017).
Methods: A long-term descriptive epidemiological study on human VL was conducted based on patient's profiles to calculated disease prevalence, geographical, spatiotemporal and seasonal distribution, distribution by age and gender, diagnosis, treatment, and treatment outcome.
Results: A total of 343 patients were reported, the average annual incidence rate was 0.73 case/100 000 population. Most cases came from the western parts of the West Bank. The number of reported males was 162 (51%), and patient's age ranged from 4 months to 16 years (average 2.5 years), of which 93.3% were $\leq$5 years old. The annual incidence rate increased between 1993–1999, peaked in 1995, and dropped as from 2002. The future projections of VL indicate that the endemic foci in most governorates are projected to disappear in the future and only the very northwest of the West Bank will be at risk of VL.
Conclusions: Visceral leishmaniasis continues to be endemic in the West Bank but not the Gaza Strip. Pentavalent antimonial sodium stibogluconate continues to be the first line treatment and physicians are recommended to consider liposomal Amphotericin B (AmBisome) for refractory patients only. Geographical, spatiotemporal and seasonal trends of VL were identified.

Introduction

Leishmaniasis is a vector-borne disease caused by protozoan parasites of the genus *Leishmania* and transmitted through the bites of infected female phlebotomine sandflies. There are three main forms of the disease; cutaneous, mucocutaneous and visceral leishmaniasis (VL). The latter, also known as kala-azar, is the most severe form and is fatal if not properly diagnosed and treated (Das et al., 2016; WHO, 2019). VL is the second largest parasitic killer in the world (after malaria), responsible for an estimated 0.7–1 million new cases and 26 000 to 65 000 deaths each year worldwide (Desjeux, 2001; WHO, 2019). In Palestine, VL is prevalent in the West Bank, mainly to western villages adjacent to the Israeli VL endemic areas, with no cases reported from the Gaza Strip (Amro et al., 2009a; Jaffe et al., 2004). The disease is zoonotic and *Leishmania infantum* is the causative agent in both humans and dogs (Amro et al., 2009a; Hamarsheh et al., 2012). The latter has been identified as a VL reservoir in Palestine, found to be infected with *L. infantum* in many endemic villages (Amro et al., 2009a; Amro et al., 2009b; Jaffe et al., 2004). Human VL was reported in infants and children, while adult cases were very rare (Amro et al., 2009a). Moreover, VL-HIV coinfection has been described in many countries around the Mediterranean Sea which is uncommon in Palestine (Monge-Maillo et al., 2014). Several risk factors associated with VL have been described. This includes poverty, malnutrition, population displacement, having a dog or other domestic animal, poor housing, weak immune system and being a household member for a previously diagnosed VL case (Amro et al., 2009a; WHO, 2019). Sandfly vectors have not been thoroughly investigated in the Palestinian endemic villages. Research studies have found numerous potential vectors abundant in Jenin and Hebron governates. This includes *Phlebotomus syriacus*, *Ph. perfiliewi*, *Ph. neglectus*, and *Ph. tobbi* (Amro et al., 2009a; Sawalha et al., 2003) which are proven vectors of *L. infantum* in the Mediterranean region (Alten et al., 2016). However, these studies were limited to a few endemic villages and a small number of collected sandflies. Hence, the role of these species in the transmission and distribution of VL in Palestine remains to be

E-mail addresses: ahmad.amro@staff.alquds.edu, ahmadymm@hotmail.com (A. Ahmad).

https://doi.org/10.1016/j.ijid.2019.10.044

determined. VL diagnosis is based on microscopy of bone marrow aspirates and clinical picture characterized by hectic fever, weight loss, hepatosplenomegaly, and anaemia. However, molecular and serological methods for diagnosis and screening of VL have been recently introduced (Amro et al., 2009a; Hamarsheh et al., 2012; Nasereddin et al., 2009). Serological studies in Jenin and Hebron revealed the presence of asymptomatic circulation of *L. infantum* among local population. Seropositivity rates among healthy children were 7.5% and 8.3% respectively (Amro et al., 2009a). Moreover, seropositivity among apparently healthy dogs in the West Bank ranged from 5.5% to 16.7 % (Abdeen et al., 2002; Hamarsheh et al., 2012). However, no comprehensive study about the prevalence and distribution of VL was done throughout Palestine. The aim of this study is to investigate the epidemiology of VL in Palestine during the period 1990 and 2017. This includes disease prevalence in human population, geographical and seasonal distribution, distribution by age and gender, diagnosis, treatment, and determination of possible factors associated with VL distribution and transmission. Moreover, spatial distribution of Palestinian VL cases and projected future distributions are explored based on climate change scenarios that could affect and occurrence and density of the sandfly vectors in Palestine.

Materials and methods

Study design

We conducted a long-term descriptive epidemiological study on human VL covering the 27-year period from 1990 to 2017 in Palestine. The study was based on Palestinian Ministry of Health (PMoH) records and collected patient profiles. This includes age, gender, geographical origin, date of diagnosis, expected starting date of infection for some cases, methods of diagnosis, treatment regime and response. VL is a reportable disease in Palestine, diagnosis and treatment is provided for free and exclusively by the PMoH and its government hospitals. There was no change in the reporting system over the time period, hence all cases of VL in Palestine were included in this study.

Study area and population

Since no VL cases were reported from the Gaza Strip, we investigated the PMoH reports in all areas in the West Bank. This includes 11 governorates; Hebron, Beithlahem, Jerusalem, Ramallah, Jericho, Tubas, Salfit, Nablus, Qalqilya, Tulkarem, and Jenin (Figure 1). The West Bank is located west of Jordan (Geographic coordinates: 32 00 N, 35 15 E). It is 5640 km^2 (including East Jerusalem) and has a population of 2,856,691 inhabitants as reported by the Palestinian Central Bureau of Statistics (PCBS) in mid-2017 (PCBS, 2019). The population is distributed across 11 governorates and ranging from 70,5053 in Hebron to 49,568 in Jericho (Figure 1).

The West Bank is characterized by great variation in its topography and altitude (ranges from −400 below the sea level in the Dead Sea area to 1020 m the highest point in Halhul, Hebron governorate). The climate is mostly Mediterranean, slightly cooler at elevated areas compared to the Dead Sea shoreline, which has a dry and hot climate. The temperature and precipitation fluctuate according to altitude. They vary from warm to hot summers, and cool to mild winters. Terrain is mostly rugged, dissected upland in the west, and flat plains descending to Jordan Valley to the east.

Data analysis

The average annual incidence rate per 100,000 population was calculated for each governorate in the West Bank between 1990–2017, based on mid-year population size estimated for each governorate in the year of infection. Distribution and frequency tables, figures and maps were plotted for each governorate, year and month of infection, and average number of cases per year/governorate. Moreover, cases were distributed by gender, age and season of infection.

Spatiotemporal analysis and projections mapping

Correlative distribution modelling was performed with the database of the Palestinian VL cases for the time period 1990–2017 as occurrence data. Conclusions were made based on these data regarding the distribution of climatically suitable areas for VL transmission based on sandfly biology.

A literature review was done to identify ecological and environmental factors affecting sandfly distribution (Amro et al., 2017; Bounoua et al., 2013; Boussaa et al., 2016); the following eight of the 19 bioclimatic variables of Worldclim (http://www.worldclim.org/bioclim) (Hijmans et al., 2005) were selected for the current and future projections: BIO1 - Annual Mean Temperature, BIO2 - Mean Diurnal Range (mean of monthly (max temp–min temp)), BIO4 - Temperature Seasonality (standard deviation *100), BIO7 - Temperature Annual Range (BIO5-BIO6), BIO10 - Mean Temperature of Warmest Quarter, BIO11 - Mean Temperature of Coldest Quarter, BIO12 - Annual Precipitation, and BIO15 - Precipitation Seasonality (Coefficient of Variation). All climate data have spatial resolution of 2.5 arc-minutes (approximately 5 km). The geographical location (longitude, latitude) was obtained using GeoLocator (http://tools.freeside.sk/geolocator/) (version 1.35).

Four modelling algorithms were applied to model the distribution of VL: GLM (Generalized Linear Model) (Guisan et al., 2002), GBM (Generalized Boosted Model) (Elith et al., 2008) and RF (Random Forest) (Breiman, 2001) included in the biomod2 R-Package version 3.3-7 (https://CRAN.R-project.org/package=biomod2) (Thuiller et al., 2016) and MAXENT (Maximum-Entropy-Modelling) (Phillips et al., 2006). Ensemble modelling (Thuiller, 2003; Thuiller et al., 2009) was performed using these four algorithms with each algorithm having the same weighting (25 %). The available VL data from 1990-2017 were used to calculate the current and the future projections (2041–2060) for VL in Palestine. For future projections, the climate model mpi-esm-lr (http://ccafs-climate.org/data_spatial_downscaling/) and the emission scenario RCP 4.5 were used. RCP 4.5 is an intermediate scenario expecting a raise in the global mean surface temperature between 1.1 °C and 2.6 °C until the end of this century (Pachauri et al., 2014). Mapping of the derived current and future projections was done using GIS software (QGIS 2.8.4-Wien, http://www.qgis.org/de/site/).

Ethics statement

All patient records and private data were anonymized and handled confidentially. The study protocol was revised and approved by the Research Ethics Committee at Al-Quds University.

Results

Palestinian ministry of health reports and VL patient's profiles were investigated for the period between 1990–2017. All cases were reported exclusively from the West Bank with no cases originated from The Gaza Strip. The total number of VL patients reported in this period was 343 patients, the average annual incidence rate was 0.73 case/100.000 population. No significant difference was reported between males and females. The number of reported males was 162 (51%) and females 154 (49%). Male to

Governorate	Population
Hebron	705,053
Jenin	312,135
Ramallah	326,008
Tulkarem	185,140
Nablus	384,953
salfit	74,790
Tubas	60,399
Qalqilya	111,425
Beithlahem	215,514
Jericho	49,568
Jerusalem	431,706
Total	**2,856,691**

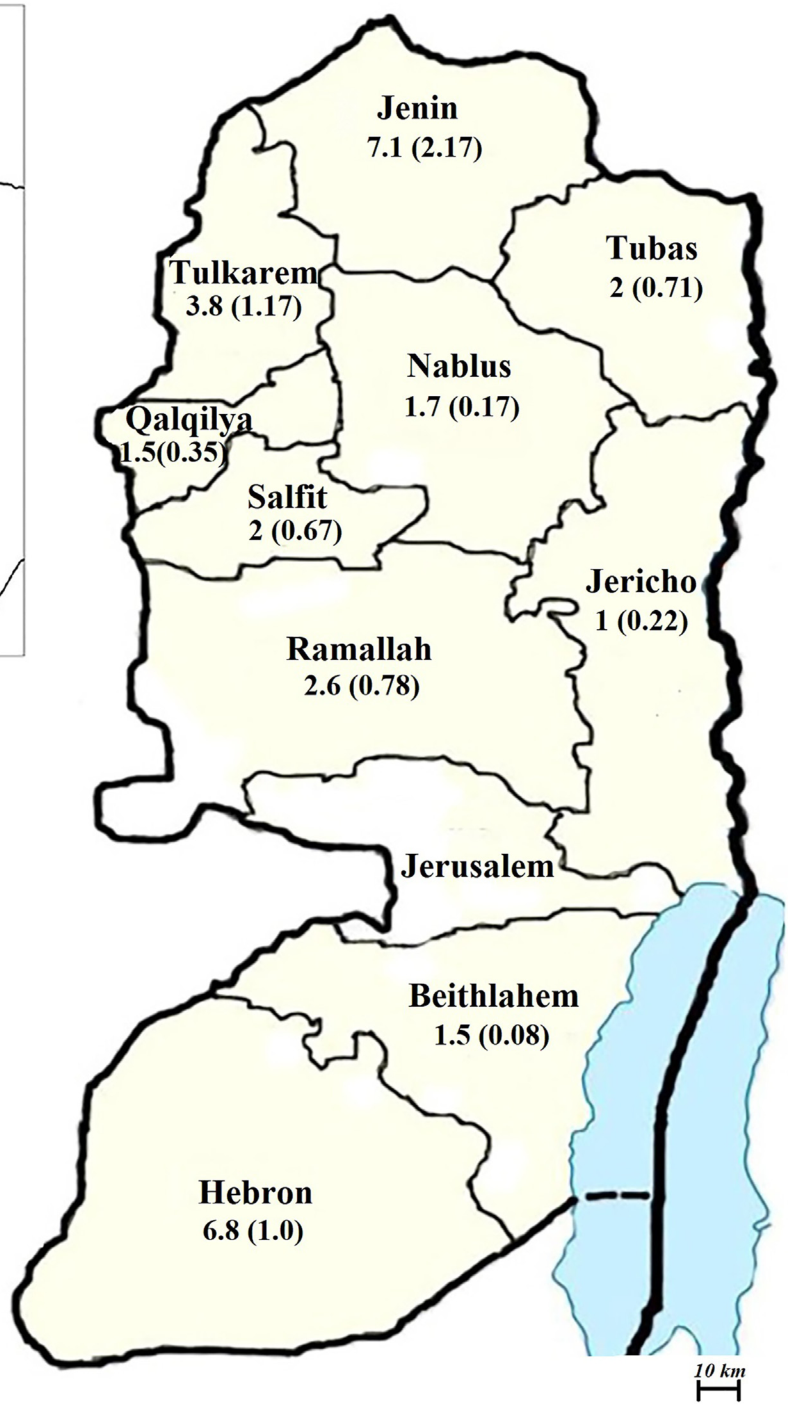

Figure 1. Distribution map of visceral leishmaniasis in Palestine between 1990 and 2017.
The geographic location of Gaza Strip and the West Bank, Palestine (top left). Distribution map of visceral leishmaniasis between 1990 and 2017 in each endemic governorate in the West Bank with no cases originate from Gaza Strip. Cases are represented by the average number of patients per year, and in parenthesis the average annual incidence rate per 100.000 population in each governorate. The table below shows the mid-year population for 2017 as estimated by the Palestinian Central Bureau of Statistics PCBS. Maps were created, adapted and edited by Adobe® Photoshop® CC 2015 and Microsoft Paint (MSPaint) 2017.

female ratio was 1.05:1. Patient age distribution at onset of illness ranged from 4 months to 16 years (average 2.5 years). Only one case from Jenin District aged 46 years was excluded from this analysis. However, 93.3% of the patients were 5 years old or younger.

Diagnosis was based on clinical symptoms, microscopic examination of giemsa-stained smears of bone marrow aspirate to confirm the presence of *Leishmania* amastigotes, and patient's residency or travel to endemic areas. In 2011, molecular and serological diagnostic approaches have been practically introduced to the Central Public Health Laboratory of the PMoH. Patients were treated successfully with intramuscular pentavalent antimonial sodium stibogluconate (Pentostam®) solution containing 10% Sb5 + (100 mg/ml) applying 10–20 mg Sb5 per kg body weight daily for 21 days. Treatment was given under supervision of medical personnel in the PMoH hospitals. Treatment failure was observed

Table 1
Distribution of visceral leishmaniasis cases in the West Bank between 1990 and 2017.

Governorate	Number of patients[a]	Percentage	AAIR/10^5 population[b]	Average number of patients/years
Hebron	116	33.8%	1.00	6.82
Jenin	107	31.2%	2.17	7.13
Ramallah	45	13.1%	0.78	2.65
Tulkarem	38	11.1%	1.17	3.80
Nablus	12	3.5%	0.17	1.71
Salfit	8	2.3%	0.67	2.00
Tubas	6	1.7%	0.71	2.00
Qalqilya	6	1.7%	0.35	1.50
Beithlahem	3	0.9%	0.08	1.50
Jericho	2	0.6%	0.22	1.00
Total	343	100.0%	0.73	12.25

[a] Total number of patients between 1990 and 2017 in each endemic governorate.
[b] Average Annual Incidence Rate per 100.000 population calculated for each governorate.

in 2005 when two cases relapsed after three weeks of Pentostam treatment and recovered after treatment with 0.25 mg/kg/day liposomal amphotericin B (AmBisome).

The most endemic governorates were Jenin and Hebron, with a total number of cases of 107 and 116 cases and an average annual incidence rate of 2.17 and 1 cases/100.000, respectively. (Figure 1 and Table 1) show all governates in the West Bank with respective distribution of VL cases represented by total and average number of cases per year and average annual incidence rate/100.1000 population for the study period. 93.3% of the total cases came from villages, compared to 6.7% who came from cities. The most endemic villages in the West Bank were Beit Ula (27 cases), Idna (14), Beit Awwa (11), Nuba (11), and Kharas (11) in the western part of Hebron, and Yamoun and Jedideh in Jenin governorate with 28, and 20 cases respectively.

Fluctuation in the incidence of VL over the studied period was investigated. The annual incidence rate increased between 1993–1999 and peaked in 1995. However, it has dropped dramatically from 2000 onwards. No cases were reported during the years 2004, 2005 and 2008 (Figure 2A).

Monthly distribution was investigated to explore seasonality trends of VL in Palestine. Higher incidence rates were reported

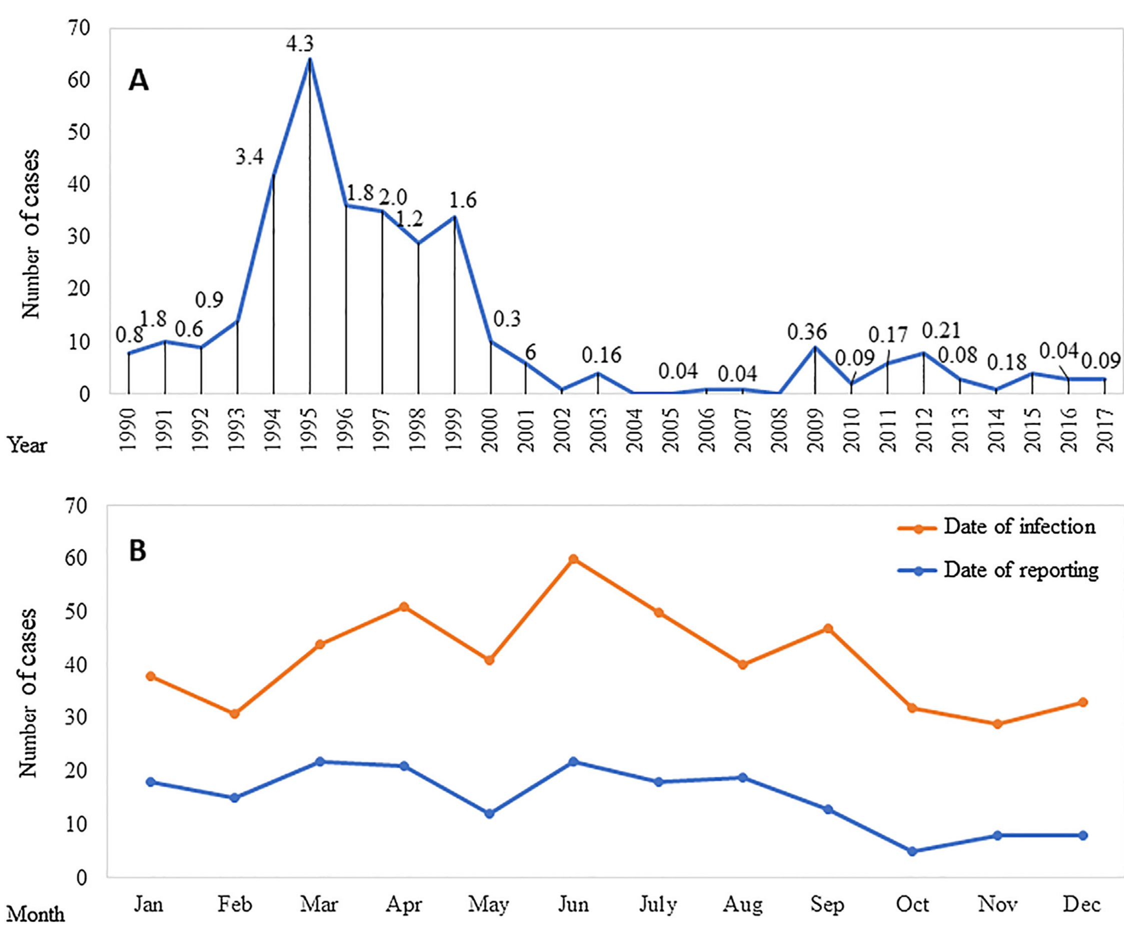

Figure 2. Annual and seasonal distribution of visceral leishmaniasis in Palestine between 1990–2017.
(A): Distribution of VL patients per year. Data labels show the annual incidence rate/100.000 population calculated for each year (B): Distribution of patients per month represented by the date of reporting as obtained from patient's profiles (upper line), and expected dates of infection (lower line). The latter was provided for some cases (181 cases) based on expectations given by patients or their parents.

during the summer season (June–August) with the highest peak recorded in June. However, the incidence rates decreased gradually during autumn (September–November) to reach the lower level during the winter season (December–February) and started a gradual increase again in spring (March–May) (Figure 2B). For some patients (181 cases), the infection date was provided together with the reporting date. The average number of days between infection and reporting dates for these patients was 36.1 (range 13–153 days). A similar pattern of seasonality was seen when cases presented by dates of infection (Figure 2B).

Spatiotemporal analysis based on climatic conditions in Palestine shows different climatic suitabilities for VL transmission in different parts of the West Bank but not in the Gaza Strip.

This analysis included all VL confirmed cases reported by Palestinian Ministry of Health for the period between 1990–2017. Figure 3 shows the present and potential future climatic suitabilities for VL cases for this period. The future projection was calculated for the years 2041-2060. The number of cases in each endemic area was added to the presence projection and indicated as different symbols in the map.

Discussion

The epidemiology and distribution of VL in Palestine over a 27-year period was investigated. A total of 343 patients were reported, of whom 93.3% were 5 years old or younger. VL in Palestine is predominant in young children. This is similar to the disease pattern of infantile Mediterranean Kala-azar where 95% of the cases are under 5 years (Aissi et al., 2015; Amro et al., 2009a). A number of studies related this pattern to the immaturity of the immune system, malnutrition in childhood and to the affinity of sandfly to this group (Dedet, 2001). Gender-related differences in VL occurrence were not significant. The trend of equal gender ratio remains the same throughout the study period and was consistent with other studies (Amro et al., 2009a). This indicates equal exposure of children (≤5 years) to the sandfly and same pattern of disease prognosis since differences at this age are not significantly apparent.

VL diagnosis was based on clinical signs and symptoms, direct microscopy of splenic or bone marrow aspirates, and patient's history of residency in or travel to endemic areas. These approaches might not be specific enough to differentiate the condition from other systemic infections. Introduction of molecular and serological diagnostic approaches by applying the ITS1 PCR-RFLP (Schonian et al., 2003) and ELISA test (Baneth et al., 1998) respectively, contributed considerably to improved sensitivity and specificity of detecting VL patients, and consequently better disease outcome and surveillance (Health Mo, 2017). Patients in Palestine are successfully treated with the first line treatment of VL (Pentostam®). However, treatment failure was reported in 2005 of two cases who recovered after being treated with liposomal Amphotericin B (AmBisome) (Amro et al., 2009a). Such treatment failure is not common in the Mediterranean region where pentavalent antimonials continue to be effective, and is more common in India and Nepal (Sundar and Chakravarty, 2015). Consequently, physicians are recommended to keep pentavalent

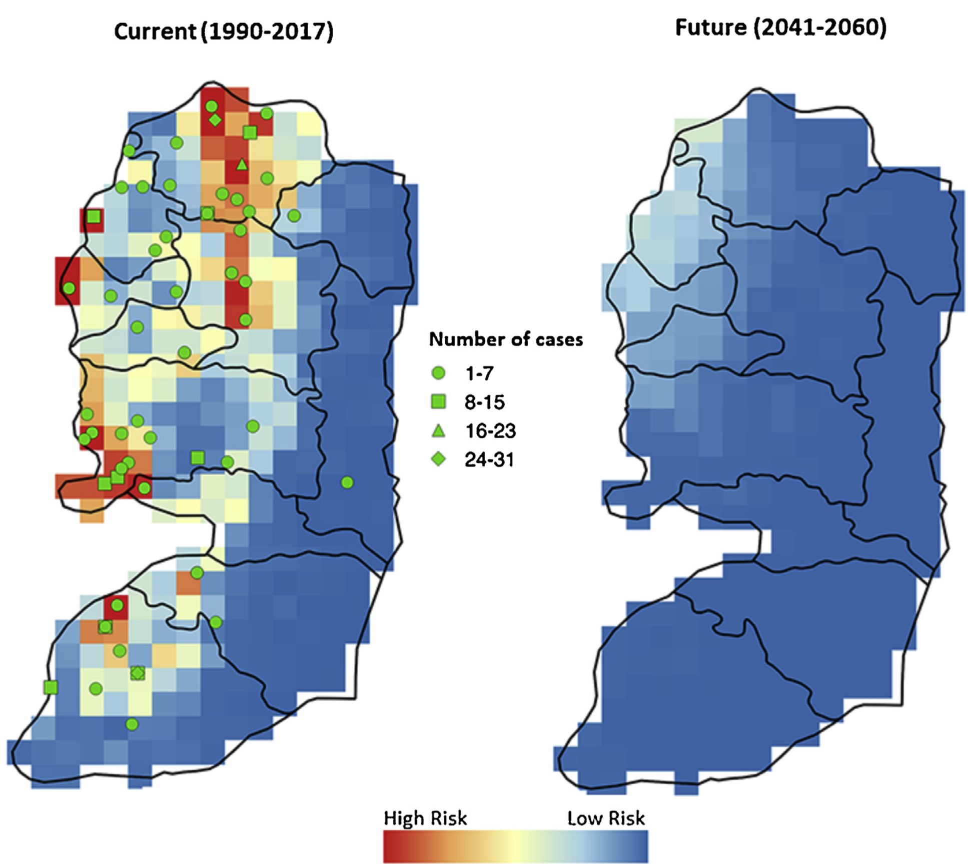

Figure 3. Spatiotemporal analysis of VL in Palestine.
Spatiotemporal analysis of the Palestinian (VL) of the time period 1990–2017. Modelled current and future climatic suitabilities for VL are shown on the maps. Projections for the presence (left map) and the future (right map) are shown. Future projection of VL in Palestine was calculated for the years 2041–2060 using the mpi-esm-lr climate model and the RCP 4.5 scenario. Number of (VL) cases in each area were added to the presence projections (indicated as different symbols in the map), showing the occurrence and the number of VL cases in the different regions of the country.

antimonial sodium stibogluconate as first line treatment of VL in Palestine and considering the liposomal Amphotericin B (AmBisome), available as antifungal agent by the PMoH, for refractory patients only.

The areas with the highest climatic suitabilities for VL in the presence are found in the western part of the West Bank. These areas represent an extension line from Jenin in the north to Hebron in the south along the West Bank and bordering the Israeli VL foci (Abdeen et al., 2002; Amro et al., 2009a; Jaffe et al., 2004) which were opened to each other until their recent separation by the Israeli wall. Generally, there is high risk of VL occurrence due to climatic suitability for the vectors along villages in these areas. These villages have similar ecology, altitude, topography, soil and cultivation activities which differ from those in the Jordan Valley and The Gaza Strip. These conditions can interfere with the sandfly population and activity, and consequently with VL incidence (Peterson and Shaw, 2003; Rotureau et al., 2006; Wasserberg et al., 2002). Other risk factors have been described in these villages, including a high number of stray and domestic dogs, low socioeconomic level, and the presence of many uncontrolled dumping sites (Abdeen et al., 2002; Amro et al., 2009a).

The number of VL patients increased between 1993–1999 and peaked in 1995. According to previous reports (Amro et al., 2009b), most of the VL cases reported during this period came mainly from recently constructed housing built during the massive expansion of these villages, following the Oslo Agreement between the Palestinians and Israel. This construction is at the periphery of villages and closer to the Israeli endemic areas where sandflies and stray dogs were abundant (Amro et al., 2009b). However, VL disappeared from the adjacent Israeli endemic areas during the period 1950–1994 (Jaffe et al., 2004) and re-emerged in 1994–1995 (the Palestinian peak) when an Israeli child and five dogs were diagnosed with VL (Baneth et al., 1998). From 2002 onward, the number of patients dropped dramatically and VL become hypo endemic in Palestine. This might be due to increased public awareness of the disease, and application of control measures such as spraying of insecticides in and around residences of VL patients and elimination of infected and stray dogs, which have led to better disease surveillance. Conversely, incidence of cutaneous leishmaniasis remains high especially in Jericho and the neighbouring areas in the Jordan Valley (Al-Jawabreh et al., 2017).

The future projections of VL indicate that the endemic foci in most governorates are projected to disappear in the future and only the very northwest of the West Bank will be at risk of VL. These projections based on climatic conditions showed that Hebron, Beithlahem, Jerusalem, Ramallah, Jericho, Tubas, Salfit and Nablus governorates are projected to offer less favourable conditions for vectors transmitting VL compared to Qalqilya, Tulkarem, and Jenin in the northwest which are at a higher level of risk. A decreasing suitability for VL can be expected in Palestine because of the projected climate changes with respect to the included bioclimatic variables. These changes include a decrease of the humidity and an increase of the temperature to a level that cannot be tolerated by VL transmitting vectors. These conditions are vital for survival, development, behaviour and activity of sandflies (Kasap and Alten, 2005). However, our results might have some drawbacks including lack of information about sandfly population density and confirmed transmitting vectors of VL in Palestine, lack of coordinates precision for each VL case, changing weather conditions year by year since our maps were done using the mean value of bio climatic variables over several years, and all bio climatic variables have only a mean value of the year and are not available for each season (winter, spring, summer and autumn).

The difference between infection dates and reporting dates of VL in Palestine ranged from 13 to 153 days (2 weeks–4 Months). This period is in agreement with the established incubation period of VL published in many endemic countries (Miro and Lopez-Velez, 2018).VL infections occur seasonally in parallel with sandfly vector abundance in Palestine, which increases from Jun to October and peaked in August (Sawalha et al., 2003). Investigation of sandfly fauna in Jenin and Hebron governorates revealed the abundance of three putative vector species transmitting VL, *Ph. perfiliewi*, *Ph. syriacus* and *Ph. Tobbi*. However, the sandfly distribution differs in the two governorates, where *Ph. perfiliewi* was most abundant in Jenin followed by *Ph. tobbi* and *Ph. (L.). syriacus* which were most abundant in Hebron governorate (Amro et al., 2009a; Sawalha et al., 2003). These differences might be due to significant variations in climatic parameters between Hebron and Jenin governorates, where the altitude ranges from (600–1011 m) and (300–500 m) respectively. However, the dynamic of sandfly fauna and its relation to the seasonal and geographical distribution of VL cases in Palestine is not well established and has to be thoroughly investigated.

In conclusion, visceral leishmaniasis continues to be endemic in the West Bank but not the Gaza Strip. The disease was shown to follow the epidemiological pattern of zoonotic infantile disease characteristic for the Mediterranean countries. *L. infantum* is the causative agent and dogs are confirmed reservoirs. However, the transmitting sandfly vector has not been yet confirmed.

Introduction of modern molecular and serological diagnostic methods contributed necessarily to better diagnosis and outcome of the disease. Pentavalent antimonial sodium stibogluconate continues to be the first line treatment and physicians are recommended to consider liposomal Amphotericin B (AmBisome) for refractory patients only. Geographical and seasonal trends of VL were identified. This can help in implementing effective control programs to reduce disease transmission.

Conflict of interest statement

The author declares no conflict of interest.

Funding source

The author did not receive any specific fund for this research.

Ethical approval

All patient records and private data were anonymized and handled confidentially. The study protocol was revised and approved by the Research Ethics Committee at Al-Quds University.

Acknowledgements

The author would like to thank the Palestinian Ministry of Health and the Arab-German Young Academy of Sciences and Humanities (AGYA) for their support. Many thanks for Prof. Marcus Frohme and Miss Olga Moskalenko for their help in spatiotemporal analysis. Many thanks also to Dr. Omar Najjar for reading and editing of the manuscript.

References

Abdeen ZA, Sawalha SS, Eisenberger CL, Khanfar HM, Greenblatt CL, Yousef O, et al. Epidemiology of visceral leishmaniasis in the Jenin District, West Bank: 1989-1998. Am J Trop Med Hyg 2002;66(4):329–33.

Aissi W, Ben Hellel K, Habboul Z, Ben Sghaier I, Harrat Z, Bouratbine A, et al. Epidemiological, clinical and biological features of infantile visceral leishmaniasis at Kairouan hospital (Tunisia): about 240 cases. Bull Soc Pathol Exot 2015;108(4):265–71.

Al-Jawabreh A, Dumaidi K, Ereqat S, Al-Jawabreh H, Nasereddin A, Azmi K, et al. Molecular epidemiology of human cutaneous leishmaniasis in Jericho and its vicinity in Palestine from 1994 to 2015. Infect Genet Evol 2017;50:95–101.

Alten B, Maia C, Afonso MO, Campino L, Jimenez M, Gonzalez E, et al. Seasonal dynamics of phlebotomine sand fly species proven vectors of mediterranean leishmaniasis caused by *Leishmania infantum*. PLoS Negl Trop Dis 2016;10(2) e0004458.

Amro A, Al-Dwibe H, Gashout A, Moskalenko O, Galafin M, Hamarsheh O, et al. Spatiotemporal and molecular epidemiology of cutaneous leishmaniasis in Libya. PLoS Negl Trop Dis 2017;11(9)e0005873.

Amro A, Azmi K, Schonian G, Nasereddin A, Alsharabati MB, Sawalha S, et al. Epidemiology of paediatric visceral leishmaniasis in Hebron district, Palestine. Trans R Soc Trop Med Hyg 2009a;103(7):731–6.

Amro A, Schonian G, Al-Sharabati MB, Azmi K, Nasereddin A, Abdeen Z, et al. Population genetics of *Leishmania infantum* in Israel and the Palestinian Authority through microsatellite analysis. Microbes Infect 2009b;11(4):484–92.

Baneth G, Dank G, Keren-Kornblatt E, Sekeles E, Adini I, Eisenberger CL, et al. Emergence of visceral leishmaniasis in central Israel. Am J Trop Med Hyg 1998;59(5):722–5.

Bounoua L, Kahime K, Houti L, Blakey T, Ebi KL, Zhang P, et al. Linking climate to incidence of zoonotic cutaneous leishmaniasis (L. major) in pre-Saharan North Africa. Int J Environ Res Public Health 2013;10(8):3172–91.

Boussaa S, Kahime K, Samy AM, Salem AB, Boumezzough A. Species composition of sand flies and bionomics of Phlebotomus papatasi and P. sergenti (Diptera: Psychodidae) in cutaneous leishmaniasis endemic foci, Morocco. Parasites Vectors 2016;9:60.

Breiman L. Random forests. Mach Learn 2001;45(1):5–32.

Das A, Karthick M, Dwivedi S, Banerjee I, Mahapatra T, Srikantiah S, et al. Epidemiologic correlates of mortality among symptomatic visceral leishmaniasis cases: findings from situation assessment in high endemic foci in India. PLoS Negl Trop Dis 2016;10(11)e0005150.

Dedet J. Leishmanies, leishmanioses. Biologie, Clinique Et Thérapeutique. Encycl Méd Chir 2001;8:506–10.

Desjeux P. Worldwide increasing risk factors for leishmaniasis. Med Microbiol Immunol 2001;190(1–2):77–9.

Elith J, Leathwick JR, Hastie T. A working guide to boosted regression trees. J Anim Ecol 2008;77(4):802–13.

Guisan A, Edwards TC, Hastie T. Generalized linear and generalized additive models in studies of species distributions: setting the scene. Ecol Model 2002;157 (2):89–100.

Hamarsheh O, Nasereddin A, Damaj S, Sawalha S, Al-Jawabreh H, Azmi K, et al. Serological and molecular survey of Leishmania parasites in apparently healthy dogs in the West Bank, Palestine. Parasites Vectors 2012;5:183.

Health Mo. Annual report Palestine 2017. In: Bitar J, editor. Health annual reports. Nablus, Palestine: Palestinian Health Information Center (PHIC); 2017.

Hijmans RJ, Cameron SE, Parra JL, Jones PG, Jarvis A. Very high resolution interpolated climate surfaces for global land areas. Int J Climatol 2005;25 (15):1965–78.

Jaffe CL, Baneth G, Abdeen ZA, Schlein Y, Warburg A. Leishmaniasis in Israel and the Palestinian authority. Trends Parasitol 2004;20(7):328–32.

Kasap OE, Alten B. Laboratory estimation of degree-day developmental requirements of Phlebotomus papatasi (Diptera: Psychodidae). J Vector Ecol 2005;30 (2):328–33.

Miro G, Lopez-Velez R. Clinical management of canine leishmaniosis versus human leishmaniasis due to *Leishmania infantum*: putting "One Health" principles into practice. Vet Parasitol 2018;254:151–9.

Monge-Maillo B, Norman FF, Cruz I, Alvar J, Lopez-Velez R. Visceral leishmaniasis and HIV coinfection in the Mediterranean region. PLoS Negl Trop Dis 2014;8(8): e3021.

Nasereddin A, Azmi K, Jaffe CL, Ereqat S, Amro A, Sawalhah S, et al. Kinetoplast DNA heterogeneity among *Leishmania infantum* strains in central Israel and Palestine. Vet Parasitol 2009;161(1–2):126–30.

Pachauri RK, Allen MR, Barros VR, Broome J, Cramer W, Christ R, et al. Climate change 2014: synthesis report. Contribution of working groups I, II and III to the fifth assessment report of the intergovernmental panel on climate change. IPCC; 2014.

PCBS. In: PCBS, editor. Estimated population in Palestine mid-year by governorate, 1997-2021. Ramallah: Palestinian Central Bureau of Statistics; 2019. http://wwwpcbsgovps/site/lang__en/803/defaultaspx?lang=en.

Peterson AT, Shaw J. Lutzomyia vectors for cutaneous leishmaniasis in Southern Brazil: ecological niche models, predicted geographic distributions, and climate change effects. Int J Parasitol 2003;33(9):919–31.

Phillips SJ, Anderson RP, Schapire RE. Maximum entropy modeling of species geographic distributions. Ecol Model 2006;190(3):231–59.

Rotureau B, Gaborit P, Issaly J, Carinci R, Fouque F, Carme B. Diversity and ecology of sand flies (Diptera: Psychodidae: Phlebotominae) in coastal French Guiana. Am J Trop Med Hyg 2006;75(1):62–9.

Sawalha SS, Shtayeh MS, Khanfar HM, Warburg A, Abdeen ZA. Phlebotomine sand flies (Diptera: Psychodidae) of the Palestinian West Bank: potential vectors of leishmaniasis. J Med Entomol 2003;40(3):321–8.

Schonian G, Nasereddin A, Dinse N, Schweynoch C, Schallig HD, Presber W, et al. PCR diagnosis and characterization of Leishmania in local and imported clinical samples. Diagn Microbiol Infect Dis 2003;47(1):349–58.

Sundar S, Chakravarty J. An update on pharmacotherapy for leishmaniasis. Expert Opin Pharmacother 2015;16(2):237–52.

Thuiller W. BIOMOD – optimizing predictions of species distributions and projecting potential future shifts under global change. Glob Change Biol 2003;9(10):1353–62.

Thuiller W, Georges D, Engler R, Breiner F, Georges MD, Thuiller CW. Package 'biomod2'. 2016.

Thuiller W, Lafourcade B, Engler R, Araújo MB. BIOMOD – a platform for ensemble forecasting of species distributions. Ecography 2009;32(3):369–73.

Wasserberg G, Abramsky Z, Anders G, El-Fari M, Schoenian G, Schnur L, et al. The ecology of cutaneous leishmaniasis in Nizzana, Israel: infection patterns in the reservoir host, and epidemiological implications. Int J Parasitol 2002;32 (2):133–43.

WHO. Visceral leishmaniasis. [Retrieved 14 March 2019].. WHO Regional Publications, Eastern Mediterranean Series; 2019. https://www.who.int/en/news-room/fact-sheets/detail/leishmaniasis.