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REVIEW

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The current epidemiology of leishmaniasis in Turkey, Azerbaijan and Georgia and implications for disease emergence in European countries

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Abstract

Leishmania spp. are sand fly-borne protozoan parasites causing leishmaniasis in humans and animals. The aim of the study was to analyse the epidemiology of leishmaniasis in Turkey, Azerbaijan and Georgia from 2005 to 2020 and evaluate the associated risk for disease emergence in European countries. It is based on an analysis of WHO and OIE reported cases between 2005 and 2020, a review of scientific articles published in SCOPUS between 2009 and 2020 and a questionnaire survey to public health and veterinary authorities in these countries. Endemic *Leishmania* spp. include *L. infantum* in the three countries, *L. major* in Azerbaijan and Turkey and *L. tropica* and *L. donovani* in Turkey. Leishmaniasis is reported in humans, animals and sand flies and incidence is spatially and temporarily variable. In the southern Caucasus and particularly in Georgia, reported incidence of human visceral leishmaniasis by *L. infantum* remains high. However, whilst Georgia experienced a gradual decrease from >4.0 cases per 100,000 population in 2005–09 to 1.13 cases per 100,000 population in 2020, the period with highest incidence in Azerbaijan, which ranged between 0.40 and 0.61 cases per 100,000 population, was 2016–2019, and no cases have so far been reported for 2020. Visceral leishmaniasis in the Southern Caucasus affects mostly young children from deprived urban areas and its closely associated to canine leishmaniasis. Turkey reported cases of visceral leishmaniasis between 2005 and 2012 and in 2016 only, and incidence ranged between 0.02 and 0.05 per 100,000 population. In contrast, the reported annual incidence of cutaneous leishmaniasis in Turkey was much greater and peaked at 7.02 cases per 100,000 population in 2013, associated to imported cases from cutaneous leishmaniasis endemic Syria. Leishmaniasis by *L. infantum* in Azerbaijan and Georgia represents a regional public and animal health challenge that requires support to improve diagnosis, treatment and control. The unprecedented rise of cutaneous leishmaniasis and the spread of *L. tropica* and *L. donovani* in Turkey is an important risk factor for their emergence in Europe, especially in Mediterranean countries where competent vectors are widespread.

KEYWORDS
Azerbaijan, Caucasus, epidemiology, Georgia, Leishmania, Turkey

1 | INTRODUCTION

Leishmaniases are a group of diseases of humans and animals caused by protozoan *Leishmania* spp. transmitted by hematophagous Phlebotomine sand flies. Two main clinical manifestations are recognized in humans, visceral leishmaniasis (VL), a life-threatening condition, and cutaneous leishmaniasis (CL), a generally more benign form (Bennis et al., 2018; Gradoni et al., 2017). Four *Leishmania* species are endemic in countries bordering the Mediterranean Sea and the Black Sea: *L. donovani* complex species (comprising *L. infantum* and *L. donovani* s.s.) causing VL and CL, and *L. major* and *L. tropica* causing mainly CL. Their main reservoir hosts include dogs for *L. infantum*, wild rodents for *L. major*, wild rodents, hyraxes and humans for *L. tropica* and humans for *L. donovani s.s*. The distribution and impact of *Leishmania* species in this region differ greatly. Whilst *L. infantum* is the most widely spread, found in countries on both sides of the Mediterranean Sea and the southern Caucasus, cases of *L. donovani s.s*. infection have only been sporadically reported in Turkey and Cyprus (Mazeris et al., 2010; Özbilgin et al., 2017) and more recently, the species was molecularly identified in *Leishmania* isolates from Israel, Palestine and Crimea (Kuhls et al., 2021). *Leishmania major* and *L. tropica* are highly endemic in North Africa, Middle East and Turkey where they are the main cause of human CL (Aoun & Bouratbine, 2014), and autochthonous disease by these species has not been described in Europe so far. However, social and environmental changes in the last two decades have affected the epidemiology of leishmaniasis in the Mediterranean region and southern Caucasus (Aoun & Bouratbine, 2014; Gradoni, 2018; Sergiev et al., 2018). War in *Leishmania* endemic Syria since 2011 has led to a rise in the incidence of CL in the country and in neighbourhood following massive migration flows (Muhjazi et al., 2019; Amr et al., 2018; El Safadi et al., 2019; Karakuş, Çizmeci et al., 2019). Moreover, a report has described infection by *L. tropica* and *L. donovani* in sand flies from refugee camps in Greece, which highlights the risk of potential spread into other areas of southern Europe where competent vectors are present (Fotakis et al., 2019) The Caucasus has also been subjected to political unrest and leishmaniasis re-emerged after the dissolution of the Soviet Union, collective economy and health services, and with it the cessation of long-standing, centralized leishmaniasis control campaigns based on elimination of animal reservoirs, insecticide application and prompt case detection and treatment (Sergiev et al., 2018; Strelkova et al., 2015).

Standing at the gates of Europe, the Middle East, North Africa and Central Asia, Turkey and southern Caucasian countries are potential sources of leishmaniasis for European countries. This review provides an epidemiological update and analyzes recent evidence for emergence of human (HumL) and animal leishmaniasis (AniL) in Turkey, Azerbaijan and Georgia between 2005 and 2020, and analyzes the potential risk for disease emergence in Europe. It is part of a larger review of leishmaniasis in the European Union and Neighbouring countries, commissioned by the European Centre for Disease Prevention and Control. The epidemiology of leishmaniasis in the Southern Caucasus and Turkey differs from southern Europe and other neighbouring endemic areas, as they have unique distributions of sand fly vector and *Leishmania* species and hybrids, some animal reservoir hosts that are not present elsewhere and different methods of animal husbandry, land use and public health and veterinary services (Sergiev et al., 2018; Strelkova et al., 2015; Kuhls et al., 2021).

Impacts

- *Leishmania infantum* is the most widely distributed species in Turkey, Azerbaijan and Georgia. Other reported species include *L. major* in Turkey and Azerbaijan, and *L. tropica* and *L. donovani s.s.* in Turkey.
- In Caucasian countries, visceral leishmaniasis is high in deprived urban areas, mostly affecting young children, and in close association to canine leishmaniasis.
- Epidemiology of leishmaniasis in Turkey has changed remarkably in the last decade associated to a mass influx of refugees infected with *Leishmania* spp.

2 | MATERIALS AND METHODS

2.1 | Data collection

Information for this review was obtained from three separate sources: (1) HumL and AniL cases reported in the World Health Organization (WHO) Global Health Observatory Data Repository (GHODR) [https://apps.who.int/gho/data/node.main.NTDLEISH?lang=en] and the World Organization for Animal Health (OIE) [https://www.oie.int/en/animal-health-in-the-world/wahis-portal-animal-health-data/], respectively, (2) a review of the scientific and grey literature published between 2009 and 2020 and (3) a questionnaire survey addressed at the public health and veterinary services of Azerbaijan, Georgia and Turkey, on the statuary notification, surveillance, diagnosis, treatment, control and emergence of human and animal leishmaniasis. The literature review included: (i) scientific articles published in the database SCOPUS, (ii) PhD and MSc thesis collected from the global Directory of Open Access Repositories (OpenDOAR), national thesis repositories and "Open Grey" web page and DART EUROPE E-THESES PORTAL, (iii) information published on national and international public health and

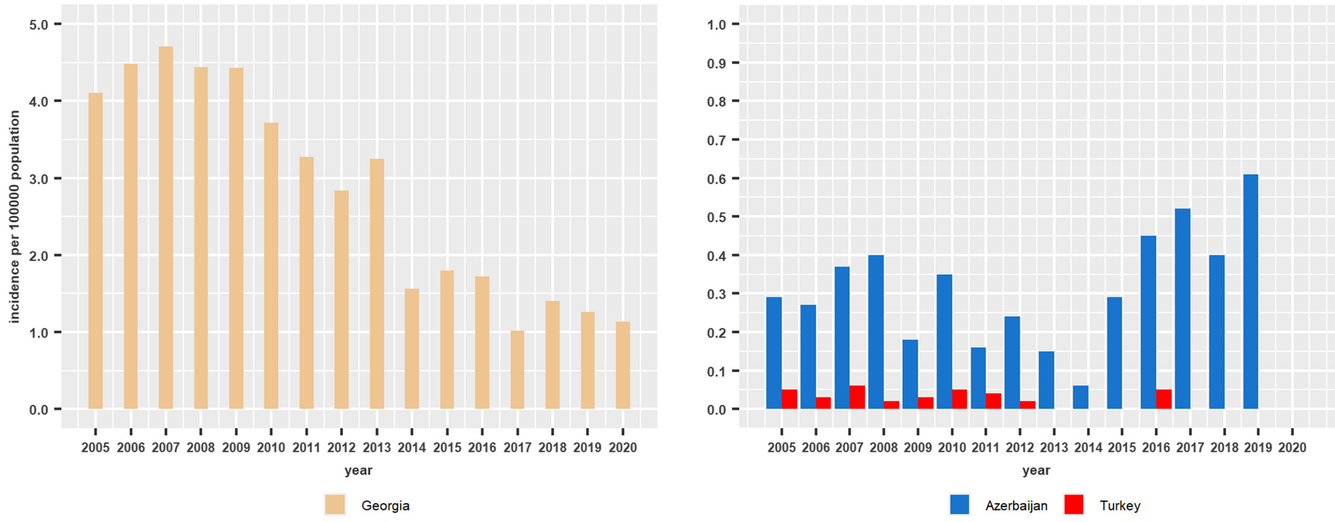

FIGURE 1 Annual cumulative incidence per 100,000 population of visceral leishmaniasis in Georgia (left) and Azerbaijan and Turkey (right) between 2005 and 2020. Data based on cases reported to the WHO Global Health Observatory Data Repository

veterinary institutions websites including the WHO, European Centre for Disease Control (ECDC), Food and Agriculture Organization (FAO), World Bank and the OIE. Search details are provided in Figure S1 and Protocols 1–4 (Appendix S1). SCOPUS searches included two Boolean search strings carried out in July 2020: one to extract data on leishmaniasis epidemiology, diagnosis, treatment and control among human and reservoir hosts (mammals), and a second one for data on *Leishmania* infection rates in the sand fly vector (Protocol 1, Appendix S1). The questionnaire survey included animal and human leishmaniasis questionnaires and part of the results obtained were published in 2021 after the literature review had been completed (Berriatua et al., 2021). Some answers specific to Azerbaijan, Georgia and Turkey, not included in Berriatua et al. (2021) are provided here.

2.2 | Data analysis and mapping

Prevalence and annual cumulative incidence rate per 100,000 people (incidence hereafter) of leishmaniasis were the percentage of reported infected/diseased per total number of individuals examined, and the number of reported cases in a year multiplied by 100,000 and divided by the country census, respectively. Annual census were obtained from The World Bank database (https://data.worldbank.org/indicator/SP.POP.TOTL). Median incidence between periods were compared using the non-parametric Kruskal Wallis test in the statistical program R (R Core Team, 2019). Significance was taken for $p<.05$ for a double-sided test.

The place of residence or diagnosis of reported leishmaniasis cases, were collected to elaborate maps of *Leishmania* spp. and clinical forms at the NUTS-3 (for Turkey) and GAUL-2 (Azerbaijan and Georgia) subnational levels, using the geographical information system ArcGIS v.10 (ESRI). Geographical coordinates were obtained from the ECDC web app. Viewer (European Centre for Disease Prevention and Control [ECDC], n.d.).

3 | RESULTS

3.1 | Information search

In the WHO GHODR human autochthonous and imported cases were reported together until 2012 and separately from 2013 onwards. Azerbaijan and Georgia reported cases every year except in 2020 when Azerbaijan did not report imported VL cases. Turkey did not report VL or CL cases between 2017–20 except in 2018. The incidence of human leishmaniasis between 2004 and 2008 has been previously analysed (Alvar et al., 2012). Here, we included data between 2005 and 2008 for a more comprehensive interpretation of the temporal trend of reported cases.

The flow of documents through the stages of the literature review are depicted in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) chart in Figure S1. Of 1147 documents included in the study involving the EU and neighbouring countries, 123 scientific articles provided information for Azerbaijan, Georgia and Turkey and among them, four articles provided information on leishmaniasis epidemiology, control and case management in more than one country. They included Berriatua et al. (2021) and Gradoni et al. (2017) who provided information for the three countries and Sergiev et al. (2018) and Strelkova et al. (2015) for the Caucasian countries. The search for PhD and MSc thesis yielded no results for the Caucasian countries while 24 theses were found in Turkey´s repositories. Information in these theses relevant to the project was published in scientific articles.

3.2 | Number of WHO and OIE reported cases of leishmaniasis and associated incidence

The number of human VL cases reported by WHO between 2005 and 2020 and the resulting annual average incidence per 100,000 population (shown here in brackets), were 1673 (2.82) in Georgia, 443 (0.32) in Azerbaijan and 245 (0.04) in Turkey (Table S1). However, the annual incidence varied greatly within and between countries (Figures 1 and 2, Table S1). In Georgia, annual incidence gradually decreased over the study period, ranging between 4.48 and 4.10 in 2005–2009, 2.84 and 3.72 in 2010–2013, and 1.07 and 1.80 in 2014–2020 ($p < .05$). In contrast, the annual VL incidence in Azerbaijan fluctuated with peaks above the period average that ranged between 0.35 and 0.40 in 2007, 2008 and 2010, and between 0.40 and 0.61 in 2016–2019, and there were no reports for 2020 (Figures 1 and 2, Table S1). In Turkey, reported VL incidence was much lower, ranging between 0.02 and 0.06, and was higher than the period average in 2005, 2007, 2010 and 2016. There were no reports of VL in 2013, 2014, 2015, 2017, 2019 and 2020 (Figures 1 and 2, Table S1).

In contrast, Turkey reported 31,580 cases of human CL between 2005 and 2016 and in 2018 (Table S1). The average annual CL incidence was 3.25, with a sharp peak of 7.06 in 2013 followed by a gradual decrease to 2.91 in 2018 (Figures 1 and 2, Table S1). Azerbaijan similarly reported 366 CL cases and the average annual incidence was 0.26. Incidence of CL in this country also fluctuated during the study period, but peaks above average did not always coincide with those of VL (Figures 1 and 2, Table S1). Only 45 cases of CL were reported by Georgia including zero cases in 2014 and between 2016 and 2020.

No animal leishmaniasis cases were reported to the OIE between 2009 and 2020 by Azerbaijan, Georgia and Turkey.

3.3 | Review of the literature and the questionnaire survey

3.3.1 | Leishmaniasis in Azerbaijan

Leishmaniasis is a notifiable disease in humans and animals and endemic species reported included *L. infantum* and *L. major*. Surveillance of clinical HumL is performed, a National Control Program (NCP) is in place and national guidelines were available for HumL diagnosis, control and treatment (Berriatua et al., 2021). Visceral leishmaniasis control actions included the use of insecticides in dogs, and CL control actions included insecticide application in the peri- and intradomiciliary environment, insecticide-treated bed nets for protection against sand fly vectors, habitat destruction of rodent host species and testing immigrants for *Leishmania* infection. Control challenges included financial and operational constrains, limited availability and high costs of laboratory diagnostic tests. Leishmaniasis was considered an emerging disease associated to insufficient control measures and to animal and people travels. Diagnosis of HumL is performed using microscopy (MIC), serological analysis including the indirect immunofluorescence test (IFAT) and the enzyme-linked immunosorbent assay (ELISA), and the polymerase chain reaction (PCR) test (Berriatua et al., 2021).

Based on records from local health centres, Agayev et al., calculated a VL prevalence (per 100,000 population) between 2014 and 2018 of 1.7 (Agayev et al., 2020). Among 170 VL cases in the later study, 85% were <5 years old, females represented 44% of them, and cases came from 33 GAUL-2 areas, particularly Barda (15%), Terter (14%), Sheki (8%) and Shamkir (8%) (Agayev et al., 2020) (Figure 3).

All CL cases are caused by *L. major* and no CL by *L. infantum* has been reported since an outbreak in Geokchay in the 1980s (Strelkova et al., 2015). At that time, CL by *L. major* was also reported from Geokchay, Agdash and Ujar. In the 1950s, *L. tropica* was responsible for over 2000 CL cases (Alvar et al., 2012) and Barda, Gyandja were notorious foci (Sergiev et al., 2018). No later reports mentioning this species have been found. *Leishmania*-HIV coinfections are very rare. Antimonials (ANT) are first-line drugs for treatment (Gradoni et al., 2017) and no information on the use of the less toxic Liposomal Amphotericin B (LAB) treatment was found.

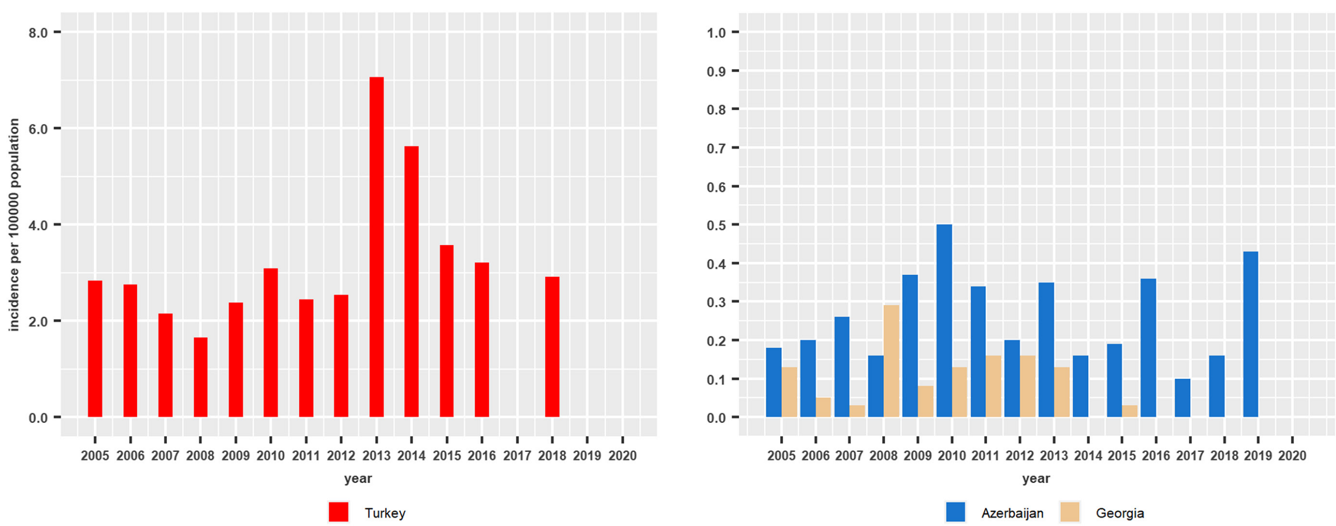

FIGURE 2 Annual cumulative incidence per 100,000 population of cutaneous leishmaniasis in Turkey (left) and Azerbaijan and Georgia (right) between 2005 and 2020. Data based on cases reported to the WHO Global Health Observatory Data Repository

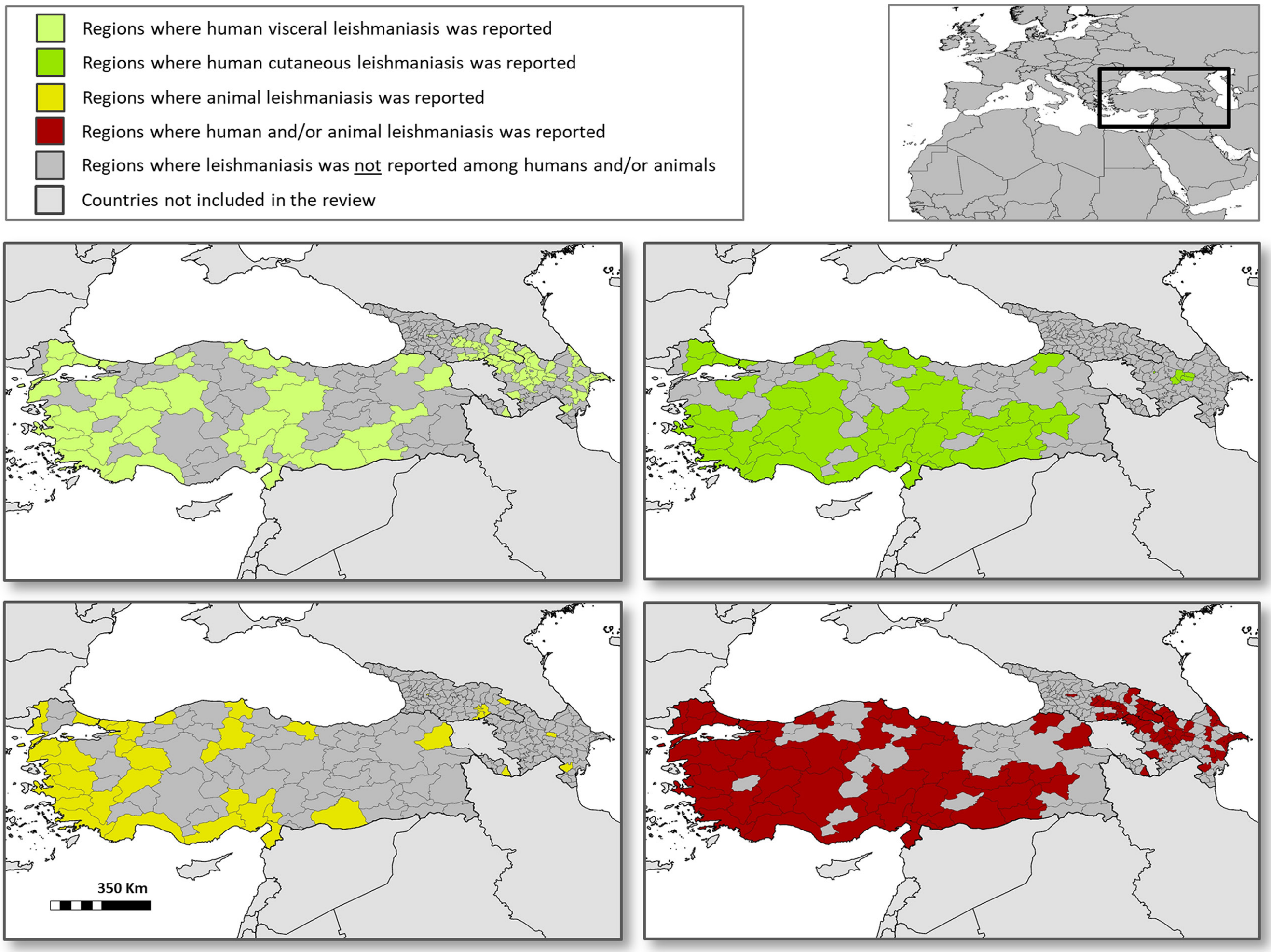

FIGURE 3 Regional distribution of human and animal leishmaniasis in Turkey, Azerbaijan and Georgia reported in the scientific literature between 2009 and 2020

Canine leishmaniasis is present in all districts where human VL occurs. Between 2014 and 2018, 4% of dogs and 1% of rodents tested for *Leishmania* rk39 antibodies using the rapid immunochromatographic test (RICT) were positive (Agayev et al., 2020). In the 1980s, the prevalence of clinical cases in stray dogs in Ordubad was 18%, and IFAT seroprevalence in dogs in Jalilabad was 17% (Strelkova et al., 2015). In the 1960s, *Leishmania* infection was detected in two foxes and one wild cat of 2388 wild animals examined (Strelkova et al., 2015). There are no reports of *Leishmania* infection in sand flies, and reported species include *P. balcanicus*, *P. kandelakii*, *P. tobbi*, *P. brevis* and *P. transcaucasicus* (Strelkova et al., 2015).

3.3.2 | Leishmaniasis in Georgia

The country is considered endemic for *L. infantum* only (Strelkova et al., 2015), and both HumL and AniL are notifiable. There is NCP involving surveillance of clinical HumL, using insecticides, treating and culling sick dogs and testing travellers and migrants (Berriatua et al., 2021). Intersectoral collaboration between public health and veterinary services takes place in endemic foci. Financial and capacity constraints (for both HumL and AniL), lack of legislation for AniL control and limited availability and high cost of diagnostic tests (AniL) and treatments (HumL and AniL), are considered the main challenges for leishmaniasis control. Diagnosis, treatment and control guidelines for HumL are available. Vector expansion as a result of climate change and other environmental changes with an impact in vectors and reservoir hosts (e.g.: urbanization, agricultural projects) followed by insufficient of control/surveillance and animal/people travelling are considered drivers for HumL emergence. Diagnostic methods for HumL include MIC, ELISA, RICT and PCR assays (Berriatua et al., 2021).

In 2018, 58% of the cases were below 5 years old, 11% between 5 and 14 years old and 31% were older, and 42% were females. HIV-coinfected patients were 5% in 2014 and 6% in 2016 (World Health Organization [WHO], 2018a). Until 2010, most of VL cases were from Tbilisi and its vicinity, and a new focus was then reported in the Western city of Kutaisi (Figure 3) (Kajaia et al., 2011; Babuadze et al., 2014). Since 2009, incidence of VL has increased in the eastern

TABLE 1 Prevalence studies of human leishmaniasis in Turkey in scientific publications from 2009 to 2020

Reference	Clinical form	Province	Study years	Age group	Environment	Diagnosis	Sample	No. tested	No. of positives	Prevalence
Gunay et al. (2014)	CL	Adana	2013	All	Rural	Microscopy	Skin aspirate	1855	80	4.3
Yentür Doni et al. (2016)	CL	Sanliurfa	2010–2012	Children	Rural, Urban	Microscopy	Skin aspirate	163,464	455	0.3
Töz et al. (2009)	VL	Denizli	-	Children, Adults	Rural	IFAT-128[a]	Serum	546	2	0.4
Ates et al. (2013)	VL	Istanbul	2008–2011	Blood Donors	Urban	Culture	Buffy coat (BC)	343	4	1.2
	VL	Istanbul	2008–2011	Blood Donors	Urban	ELISA	Serum	343	9	2.6
	VL	Istanbul	2008–2011	Blood Donors	Urban	IFAT	Serum	343	7	2.0
	VL	Istanbul	2008–2011	Blood Donors	Urban	Culture, ELISA, IFAT	BC, Serum	343	21	6.1
Ates et al. (2012)	VL	Istanbul	-	Blood Donors	Urban	ELISA	Serum	188	1	0.5
	VL	Istanbul	-	Blood Donors	Urban	IFAT-128[a]	Serum	188	6	3.2
	VL	Istanbul	-	Blood Donors	Urban	RICT	Serum	188	0	0.0
Sari et al. (2015)	VL	Kars	2006	Children	Rural	IFAT	Serum	290	0	0.0

[a]Cut-off dilution.

Kakheti region (Babuadze et al., 2016) and in Kvemo Kartli south of Tbilisi (Berriatua et al., 2021) (Figure 3).

Antibody prevalence in randomly selected 1 to 14 years old children in Tbilisi between 2006 and 2008, assessed with the direct agglutination test (DAT), was 7% (Giorgobiani et al., 2011). In a later study in 2012 in Tbilisi and Kutaisi, the prevalence of asymptomatic human infection analysed with the Leishmanin Skin Test, was 15% and 7%, respectively (Babuadze et al., 2014). In Kakheti in 2014, 1% of people from households with a historical case of VL were seropositive by the rk-39 RICT (Babuadze et al., 2016). Antimonials are first-line treatment for VL with a cure rate 96% (Gradoni et al., 2017) and LAB is available (Berriatua et al., 2021).

Canine leishmaniasis is common in areas with HumL. Seroprevalence in dogs from Tbilisi in 2006–08 analysed with the rk39 RICT, was 15% in stray and 18% in household animals, and 1–3% had clinical signs (Giorgobiani et al., 2011). In a subsequent study in Tbilisi in 2011 and 2012, rk39 RICT seroprevalence was 24% and 16% in household and stray dogs and 3% of wild canids, respectively (Babuadze et al., 2014). In Kakheti in 2014, seroprevalence using the rk39 test in household dogs was 16% (Babuadze et al., 2016). Antibody ELISA is also used for CanL diagnosis, and treatment include the antimonial meglumine antimoniate (MA) and allopurinol (Berriatua et al., 2021).

In the VL focus area of the Tbilisi district in 2008–10, *L. infantum* DNA was detected in 2% of *P. kandelakii* and 5% of *P. balcanicus* sand flies (Giorgobiani et al., 2012). In Tbilisi and Kutaisi in 2011, infection was detected in 6% of *P. kandelakii*, 2% of *P. balcanicus* and 1% of *P. halepensis* (Babuadze et al., 2014). In Kvareli in 2014, 7% of *P. balcanicus* were infected (Babuadze et al., 2016). Other species reported by these authors include *P. sergenti* and *P. wenyoni* (Giorgobiani et al., 2012; Babuadze et al., 2014, 2016).

3.3.3 | Leishmaniasis in Turkey

Autochthonous *Leishmania* spp. includes *L. infantum*, *L. donovani* s.s., *L. tropica* and *L. major* and leishmaniasis notification is mandatory in humans only (Berriatua et al., 2021). Turkey has a passive surveillance scheme for clinical HumL and a NCP for *L. major* and *L. tropica* that includes screening programs for CL in endemic areas, testing travellers and migrants and use of insecticides and mechanical barriers for vectors in the peri- and intradomiciliary environment. The Leishmaniasis control program is part of the "One Health" Turkish Zoonotic Diseases Action Plan (2019–2023) involving the Ministries of Health and Agriculture and Forestry. Official guidelines are available for HumL diagnosis and treatment and not for control. Main HumL control challenges are lack of vaccines, followed by absence of legislation against culling infected/sick dogs/animals and followed by difficulty in environmental interventions to destroy the habitat of reservoirs and collaborative constraints between stakeholders. The main challenge for AniL control is other disease priorities. No diagnostic, treatment and control guidelines are available for AniL. Diagnosis of HumL is based on MIC, PCR, ELISA, IFAT, RICT and DAT (Berriatua et al., 2021).

The age distribution of VL cases in 2014, 2016 and 2018 ranged from 0–32% for <5 years old, 22–30% for 5–14 years old and 42–68% for >14 years old for VL. Likewise, for CL, these ranges were 0–18% for <5 years old, 33–34% for 5–14 years old and 48–64% for >14 years old (World Health Organization [WHO], 2016, 2018b) (WHO Leishmaniasis country profile – 2018 for Turkey, unpublished).

Of 81 NUTS-3 subdivisions (provinces) in Turkey, CL has been reported from 32 and VL from 28 (Figure 3). The provinces where CL cases were most common, in order of frequency, were Sanliurfa, Adana, Gaziantep, Hatay, Antalya and Diyarbakir, and for VL cases, Adana, Antalya, Hatay, Izmir and Denizli. *Leishmania infantum*, *L. tropica*, *L. major* and *L. donovani* were detected from 30, 25, 11 and 10 provinces, respectively. All four species were reported from Adana, Antalya, Diyarbakır, Hatay, Manisa, Mardin and Sanliurfa (Ates et al., 2013; Dinçer et al., 2012; Gülez et al., 2011; Koltas et al., 2014; Özbilgin et al., 2016, 2019; Ozerdem et al., 2009; Tok et al., 2009; Toz et al., 2013; Yazar, Kuk, Cetinkaya, & Sahin, 2013a; Yazar, Kuk, Cetinkaya, Uyar, & Sahin, 2013b; Yentur Doni et al., 2020).

The prevalence of VL and CL in randomly selected humans investigated in five provinces between 2006 and 2013 with different diagnostic methods, ranged between 0.3–4.3% for CL (Table 1) (Gunay et al., 2014; Yentür Doni et al., 2016) and 0–6.1% for VL (Akpolat et al., 2014; Ates et al., 2012, 2013; Töz et al., 2009).

Leishmania-HIV coinfections are infrequent. First-line treatment for VL, included in the national medicine list is with ANT, with a 95% cure rate, and second-line treatment is with LAB (Gradoni et al., 2017).

Canine leishmaniasis has been reported from 21 provinces (Table 2) (Aydenizöz et al., 2010; Balcioğlu et al., 2009; Bolukbas et al., 2016; Doğan et al., 2014; Düzbeyaz et al., 2016; Karakuş et al., 2015; Koenhemsi et al., 2020; Pasa et al., 2009; Sari et al., 2015; Tok et al., 2009; Toz et al., 2013; Utuk et al., 2018), and 17 studies investigated CanL prevalence in randomly selected dogs from different environments and locations using a variety of diagnostic tests (Atasoy et al., 2010; Aydenizöz et al., 2010; Bakirci et al., 2016; Balcioğlu et al., 2009; Beyhan et al., 2016; Bilgin et al., 2015; Bolukbas et al., 2016; Dincer et al., 2016; Doğan et al., 2014; Düzbeyaz et al., 2016; Karakuş, Arserim, et al., 2019; Karakuş et al., 2015; Koenhemsi et al., 2020; Sari et al., 2015; Tok et al., 2009; Töz et al., 2009; Utuk et al., 2018). Seroprevalence using the IFAT ranged from 0% to 27% and was ≥19% in Adana, Aydin, Denizli, Eskisehir and Mersin. PCR prevalence in blood samples ranged between 2–10% and was lower than IFAT seroprevalence in dogs tested with both techniques. In contrast, prevalence assessed by PCR in conjunctival swabs was 42% in Adana and 25% in Izmir. *Leishmania infantum* was the only species identified in four studies that included parasite identification.

Similarly, *Leishmania* prevalence in randomly selected cats was investigated in five studies mostly in Western Turkey (Table 2) (Can et al., 2016; Dincer et al., 2015; Dincer et al., 2016; Karakuş, Arserim, et al., 2019; Paşa et al., 2015). Prevalence in cats from Izmir was 15% by IFAT, 11% by ELISA and 0.5% by PCR in blood samples (5 cats infected with *L. tropica* and 1 cat with a mixed *L. tropica* and *L. infantum* infection). In other studies, PCR prevalence in conjunctival samples or blood ranged between 0–8.8% and cats were infected by *L. infantum*, *L. tropica* and *L. major* (Table 2).

Leishmania spp. prevalence in 712 wild rodents from 30 provinces analysed by PCR in spleen, liver and lung samples was 1.12% (Karakuş et al., 2020). Species typing revealed five *L. infantum*, two *L. tropica* and one *L. major*. *Leishmania major* and *L. infantum* DNA were detected in *Apodemus* spp. from Zonguldak, *L. tropica* DNA was found in *Meriones* spp. and *Gerbillus dasyurus* from Adana and Hatay provinces.

Leishmania spp. infection rates in sand flies analysed individually ranged between 0% and 1.96% (Table 3) (Bolukbas et al., 2016; Özbel et al., 2016; Svobodová et al., 2009; Töz et al., 2009). Similarly, minimum infection rates in pooled sand fly samples were between 0.63% and 5.17% (Demir & Karakuş, 2015; Karakuş, Arserim, et al., 2019; Karakuş et al., 2017; Kavur et al., 2018; Kavur et al., 2015; Özbel et al., 2020).

4 | DISCUSSION

Understanding the spatial and temporal distribution of infections in the population allows evaluating their impact, the efficacy of control actions and possible future interventions. The key to this is having accurate information on disease frequency. Case underreporting is inherent to leishmaniasis and in humans is particularly important for CL (Alvar et al., 2012). Although it was not possible to ascertain the quality of the HumL data reported to the WHO, it was presumably, mostly subjected to a constant bias across time, allowing to analyse temporal trends without incorporating further, large bias. Data on AniL from the OIE was scarce clearly indicating severe underreporting and a need to strengthen AniL surveillance and reporting.

Our review confirms that *L. infantum* is the most widely distributed species, present in 29 provinces in Turkey, and in Azerbaijan and Georgia. In contrast to Turkey and southern European countries, the incidence of VL in the Caucasian countries is high in urban environments, and children below 5 years old remain the most affected. Combinations of interlinked factors related to poverty are responsible for this situation (Strelkova et al., 2015). The presence of infected stray and owned dogs lacking preventive insecticide treatments, many with clinical leishmaniasis which is associated with high parasite load, are the main source of *L. infantum* for the vector, and would explain the relatively high infection rates in vectors in some endemic areas in Georgia (Babuadze et al., 2014, 2016; Giorgobiani et al., 2012). Inadequate housing and sanitary conditions allow sand flies to thrive, and malnutrition, which undermines the immune system, is a risk factor for leishmaniasis (Nweze et al., 2020). Because *L. infantum* epidemiology in the Southern Caucasus is associated to the local dog infection prevalence and insufficient resources to prevent transmission, the situation there is unlikely to have a major impact on the epidemiology of *L. infantum* infection in Europe. Further support to improve case diagnostic and treatment and disease control is required to decrease *L. infantum* incidence in this region.

TABLE 2 Prevalence studies of canine and feline leishmaniasis in Turkey by province in scientific publications from 2009 to 2020

Reference	Origin	Province	Diagnostic Test	Diagnostic sample	No. tested	No. of positives	Prevalence
CANINE							
Dincer et al. (2016)	Urban	Mersin	PCR	Blood	160	2	1
Bilgin et al. (2015)	Kennel, Household	Istanbul	PCR	Blood	246	21	9
Karakuş, Arserim, et al. (2019)	Kennel	Izmir	PCR	Conjunctival swab	44	11	25
Karakuş et al. (2015)	Rural	Adana	IFAT-80[a]	Serum	206	56	27
	Rural	Adana	PCR	Conjunctival swab	206	86	42
Bakirci et al. (2016)	Kennel	Aydin	IFAT	Serum	41	9	22
	Kennel	Aydin	PCR	Blood	41	4	10
Töz et al. (2009)	Shelter, Rural	Denizli	IFAT-128[a]	Serum	140	29	21
Doğan et al. (2014)	Urban	Eskisehir	IFAT-64[a]	Serum	185	35	19
Utuk et al. (2018)	Urban	Mersin	IFAT-40[a]	Serum	16	3	19
Atasoy et al. (2010)	Shelter	Aydin	IFAT-128[a]	Serum	78	11	14
	Shelter	Mugla	IFAT-128[a]	Serum	100	12	12
Utuk et al. (2018)	Urban	Kocaeli	IFAT-40[a]	Serum	38	4	11
Bakirci et al. (2016)	Kennel	Manisa	IFAT	Serum	42	4	10
	Kennel	Manisa	PCR	Blood	42	1	2
Balcioğlu et al. (2009)	Shelter	Antalya	IFAT-128[a]	Serum	176	14	8
Bakirci et al. (2016)	Kennel	Izmir	IFAT	Serum	108	8	7
	Kennel	Izmir	PCR	Blood	108	5	5
Sari et al. (2015)	Stray	Kars	IFAT-128[a]	Serum	165	12	7
Utuk et al. (2018)	Urban	Sakarya	IFAT-40[a]	Serum	20	1	5
Atasoy et al. (2010)	Shelter	Izmir	IFAT-128[a]	Serum	65	3	5
	Shelter	Manisa	IFAT-128[a]	Serum	26	1	4
Tok et al. (2009)	Shelter	Canakkale	IFAT-64[a]	Serum	27	1	4
Koenhemsi et al. (2020)	Urban	Istanbul	IFAT-40[a]	Serum	171	5	3
Aydenizöz et al. (2010)	Rural	Kirikkale	IFAT-128[a]	Serum	50	1	2
	Rural	Kirikkale	Microscopy	Blood	50	0	0
Beyhan et al. (2016)	Kennel	Hatay	IFAT-128[a]	Serum	124	1	1
Bolukbas et al. (2016)	Shelter	Sinop	ELISA	Serum	240	1	0
	Shelter	Sinop	PCR	Lymph Node	240	1	0
Düzbeyaz et al. (2016)	Kennel	Edirne	IFAT-128[a]	Serum	37	0	0
FELINE							
Can et al. (2016)	Urban	Izmir	ELISA	Serum	1101	120	10.9
	Urban	Izmir	IFAT	Serum	1101	168	15.3
	Urban	Izmir	PCR	Blood	1101	6[1]	0.5
Karakuş, Arserim, et al. (2019)	Shelter	Izmir	PCR	Conjunctival swab	19	1[2]	5.3
Dincer et al. (2016)	Urban	Icel	PCR	Blood	50	0	0.0
Dincer et al. (2015)	Urban, shelter	Icel	PCR	Blood	22	1[2]	4.6
Paşa et al. (2015)	Urban and rural	West Turkey	PCR	Blood	147	13[3]	8.8

Note: [1]*L. tropica*: 5 cats, *L. infantum* & *L. tropica*: 1 cat. [2]*L. infantum*. [3]*L. tropica*: 9, *L. major*: 4.

[a]Cut-off dilution.

TABLE 3 Sand fly infection rates in Turkey by province in scientific publications from 2009 to 2020

Reference	Province	Sand fly species	Sample type	Diagnostic method	No.	Positives	Percentage infected
Özbel et al. (2016)	Aydin	*Sergentomyia dentata*	Individual	Dissection	51	1	1.96
Svobodová et al. (2009)	Osmaniye	*Phlebotomus tobbi*	Individual	Dissection	579	11	1.90
	Adana	*Phlebotomus tobbi*	Individual	Dissection	551	2	0.36
Özbel et al. (2016)	Aydin	*Phlebotomus tobbi*	Individual	Dissection	571	1	0.18
	Aydin	*Phlebotomus tobbi*	Individual	PCR	571	1	0.18
Bolukbas et al. (2016)	Sinop	Unknown	Individual	PCR	18	0	0.00
Töz et al. (2009)	Denizli	Unknown	Individual	Dissection	180	0	0.00
Karakuş et al. (2017)	Aydin	*Phlebotomus neglectus*	Pool	PCR	NA	3	5.17
	Aydin	*Phlebotomus tobbi*	Pool	PCR	NA	3	3.84
Demir & Karakuş (2015)	Sanliurfa	*Phlebotomus sergenti*	Pool	PCR	111	4	3.60
Özbel et al. (2020)	Mardin	*Phlebotomus sergenti*	Pool	PCR	38	1	2.63
Kavur et al. (2015)	Adana	*Phlebotomus tobbi*	Pool	PCR	131	2	1.53
Karakuş, Arserim, et al. (2019)	Izmir	*Phlebotomus tobbi*	Pool	PCR	229	3	1.31
Kavur et al. (2015)	Adana	*Phlebotomus papatasi*	Pool	PCR	94	1	1.06
Karakuş et al. (2017)	Aydin	*Sergentomyia dentata*	Pool	PCR	NA	1	1.03
Kavur et al. (2018)	Afyon	*Phlebotomus halepensis*	Pool	PCR	433	3	0.69
	Nidge	*Phlebotomus papatasi*	Pool	PCR	320	2	0.63

Proposed actions would include provision of surveillance, diagnostic and control guidelines and diagnostic and treatment capabilities. Incorporating LAB as the first-line drug would reduce treatment toxicity associated to antimonial compounds as well as the risk of treatment failures and development of resistance to antimonial compounds.

The high increase in the incidence of human CL in Turkey in 2013–16 was associated with millions of refugees arriving from CL endemic Syria. Both *L. tropica* and *L. major* are diagnosed in refugees with a predominance of *L. tropica*, which is also the most common CL species in Turkey (Özbilgin et al., 2019). Autochthonous *L. major* infections were diagnosed in Turkey for the first time also during this period, and *L. major* reports were available from 11 provinces by 2020, suggesting the species is spreading (Özbilgin et al., 2016). The reasons for *L. major*'s recent incursion and dissemination in Turkey may also be linked to extended *Phlebotomus papatasi* vector activity periods as a result of climate change, possibly facilitating *L. major* transmission, and to improved diagnosis (Özbilgin et al., 2016). In contrast to Europe, Turkey hosts wild rodent species such as *Meriones* spp. and *Gerbillus* spp. able to sustain *L. major* transmission in the population. However, in Turkey *L. major* in rodents has so far only been detected in *Apodemus* spp. mice whose role as primary reservoirs of *L. major* has not been demonstrated (Karakuş et al., 2020). This is an issue that requires further investigation given that *Apodemus* spp. are widespread throughout the Mediterranean Basin including southern European countries where *P. papatasi* is ubiquitous.

Turkey is the only country in the study area where *L. donovani s.s* is endemic and it was first reported in 2017 (Özbilgin et al., 2017). The origin of this infection is not known. The specific strain in Turkey is similar to *L. donovani* strains circulating in North Cyprus according to microsatellite analyses, and differ from those in the Indian continent and East Africa where *L. donovani* is highly endemic (Gouzelou et al., 2012). Our review suggests that *L. donovani* distribution is expanding as it has now been reported from 10 Turkish provinces. Differentiating *L. donovani* complex species based on biochemical and genetic analysis is, however, challenging and a limitation for clinical and epidemiological investigations (Fernández-Arévalo et al., 2020).

The fact that people are the primary reservoir of *L. donovani* and *L. tropica* adds further concern for the spread of these parasites into continental areas in southern European countries where competent vectors are widespread. Turkey is presently the main migration route to Europe for Middle East, Caucasian and Asian refugees and migrants; it is a major tourist destination for Europeans and there are almost 5 million Turkish people living in different European countries of which some visit Turkey frequently. Northern European countries frequently report imported leishmaniasis cases from Turkey and other Mediterranean countries (Mockenhaupt et al., 2016). As previously mentioned, there is now evidence of *L. tropica* and *L. donovani* infections in *Phlebotomus* spp. in refugee camps in Greece (Fotakis et al., 2019).

Leishmaniasis studies in humans, dogs and cats in Turkey provided relevant diagnostic, clinical and epidemiological information.

Differences in the estimated prevalence of *Leishmania* in dogs, cats and sand flies from different areas of Turkey reflect variability in infection rates according to the populations examined and the sensitivity and specificity of the diagnostic tests used. There is need for *Leishmania* diagnostic test standardization and agreement on gold standards in animals to allow accurate quantitative estimations and comparisons between populations and geographical areas. Furthermore, infection of cats with *L. infantum*, *L. tropica* and *L. major* proves that they are susceptible to these *Leishmania* spp. infections (Paşa et al., 2015; Pennisi, 2015), and more studies are needed to investigate cat's role in leishmaniasis epidemiology (Pennisi & Persichetti, 2018).

In summary, the epidemiology of leishmaniasis in Turkey has experienced remarkable changes in the last decade associated to a mass influx of people infected with *Leishmania* spp. Infections by *L. tropica* and *L. donovani* are presently not endemic in European countries but the parasites have already been demonstrated in sand flies in Greece and there is a risk that they will spread into other areas of Europe. Control and preventive measures need to be put in place to prevent this from happening. They include organizing schemes to systematically diagnose and treat infected people coming from endemic areas and improving sanitary conditions in refugee camps to reduce vector transmission (Fotakis et al., 2019). Surveillance and reporting of HumL and AniL in particular needs to strengthen throughout the study region to allow investigating the evidence for leishmaniasis emergence on national and subnational levels.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data used in this literature review are available from the references cited.

DISCLAIMERS

Yves Van der Stede is currently employed with the European Food Safety Authority (EFSA) in the ALPHA Unit that provides scientific and administrative support to EFSA's scientific activities in the area of Animal Health and Welfare. The positions and opinions presented in this article are those of the authors alone and are not intended to represent the views or scientific work of EFSA.

ETHICAL APPROVAL

No animals were used in this literature review.

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