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## Knock, knock, knocking on Europe's door: Threat of leishmaniasis in Europe with a focus on Turkey

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### ABSTRACT

Leishmaniasis epidemiology is currently undergoing substantial transformations in both Turkey and Europe, signifying potential implications for public health. This review analyzes the evolving patterns within Turkey and their potential ramifications for Europe. Within Turkey, the dynamics of leishmaniasis are undergoing noteworthy alterations, manifesting in a rise in cutaneous leishmaniasis (CL) cases and the emergence of *Leishmania major* and *Leishmania donovani*. These transformations are predominantly driven by factors such as the distribution of vectors, human activities, climate fluctuations, and migration. Across Europe, particularly in countries within the Mediterranean basin, leishmaniasis is endemic, primarily attributed to *Leishmania infantum*. Recent evidence suggests a resurgence of the disease even in previously non-endemic areas, propelled by climate change, urbanization, and migration. The changing landscape of leishmaniasis in Turkey carries direct implications for Europe. The presence and distribution of *Leishmania tropica*, *L. major*, and *L. donovani* raise concerns regarding cross-border transmission. Turkey's strategic position along migration routes further compounds the risk, alongside the facilitative effects of climate change and host mobility. Embracing a One Health approach with public awareness campaigns should be a priority. To ensure the protection of public health in Europe, it is imperative to adopt a proactive approach by establishing robust surveillance mechanisms, implementing preventive measures, and cultivating collaboration with Turkey. The invaluable experience, strategic geographical location, and well-established infrastructure of Turkey make this collaboration crucial in effectively addressing the evolving dynamics of leishmaniasis and its potential impacts on Europe.

### 1. Introduction

Leishmaniasis, a neglected tropical disease caused by protozoan parasites of the genus *Leishmania*, poses a significant public health concern globally (Mohan et al., 2022). With its diverse clinical manifestations and widespread distribution, leishmaniasis remains a challenging and complex disease to control (Sasidharan and Saudagar, 2021). While traditionally considered endemic in tropical and subtropical regions, recent evidence suggests an alarming increase in its incidence and geographical spread, bringing the threat of leishmaniasis to Europe's doorstep (Van der Auwera et al., 2022).

Turkey, located at the crossroads of Europe and Asia, has experienced notable changes in the epidemiology of leishmaniasis in recent years, making it a pertinent example for Europe (Özbilgin et al., 2022). Previously considered an endemic region for leishmaniasis, Turkey has witnessed shifts in the disease dynamics, including both geographical

expansion and changes in the clinical presentation of cases (Özbilgin et al., 2017). These changes are primarily attributed to factors such as vector distribution, human activities, climate change, and population movement (Özbilgin et al., 2019).

The main purpose of this review is to emphasize the potential threat of leishmaniasis in Europe, based on recent changes in its epidemiology in Turkey. This country is an important case study due to its strategic location on migration routes to Europe and its similar climate to many European regions. By exploring the leishmaniasis situation in Turkey and its implications, this review aims to increase awareness about the possible risks and challenges that Europe could encounter with leishmaniasis.

### 2. Current overview of leishmaniasis in Europe

Leishmaniasis is endemic in all southern countries of Europe,

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including Greece, Italy, Portugal, Spain, and Turkey. With an average of approximately 700 autochthonous human cases reported annually across multiple countries, and the number increasing to around 3950 cases when considering Turkey, *L. infantum* is identified as the causative agent of the disease, while domestic dogs act as the primary reservoir hosts, exhibiting a seroprevalence of up to 30% (Rombolà et al., 2021).

To fully comprehend leishmaniasis in different parts of Europe, it is essential to investigate the unique aspects of the disease epidemiology in each country. By examining country-specific data and characteristics, we can gather valuable insights into how prevalent, widespread, and impactful leishmaniasis is in various regions of Europe.

Spain has long been considered an endemic country for leishmaniasis, with the majority of cases caused by *L. infantum* (Mas et al., 2020). Visceral leishmaniasis (VL) is primarily endemic in the southern and eastern regions, particularly in the Mediterranean basin. Recently, there have been concerns regarding the re-emergence of leishmaniasis in previously non-endemic regions of Spain, including Catalonia and Navarra (Fernández-Arévalo et al., 2021). Climate change, increasing urbanization, and human activities are believed to contribute to this spread (ECDC, 2022).

Italy is another country heavily affected by leishmaniasis, predominantly caused by *L. infantum*. The disease is endemic throughout the country, with higher prevalence observed in southern and central regions (Giancetti and Montomoli, 2020; Moirano et al., 2022). Historically, regions such as Campania, Calabria, Sicily, and Apulia have reported the highest number of cases. However, there has been a documented increase in the incidence of leishmaniasis in previously non-endemic areas of Italy, particularly in northern regions such as Lombardy, Piedmont, and Veneto (Gradoni et al., 2022). This expansion is likely associated with the introduction of infected dogs from endemic regions and the spread of competent sand fly vectors (Morosetti et al., 2020).

Greece has a long history of leishmaniasis, primarily caused by *L. infantum*. The disease is endemic in various regions, including mainland Greece and several islands (Maia et al., 2023). The highest incidence rates are observed in the southern parts of the country, such as the Peloponnese, Crete, and the Ionian Islands (Kantzanou et al., 2023). However, there have been reports of leishmaniasis cases in previously non-endemic areas of Greece, such as the northern regions of Thessaly and Epirus (Symeonidou et al., 2021). This expansion is attributed to changes in environmental conditions, urbanization, and increased movement of infected individuals and reservoir hosts (Mann et al., 2021).

Portugal has a significant burden of leishmaniasis, primarily caused by *L. infantum*. The disease is endemic throughout the country, with higher incidence rates reported in the majority of territorial subdivisions (Maia et al., 2023). There have been reports of emergence and re-emergence of leishmaniasis in specific regions of Portugal. For instance, in recent years, the central region of Lisbon has experienced an increase in the number of cases, indicating an expansion of the disease beyond its traditionally endemic areas (Maia et al., 2022).

In recent years, there has been evidence of the re-emergence of leishmaniasis in previously endemic regions as well as the emergence of the disease in previously non-endemic regions of Europe (ECDC, 2022). This resurgence can be attributed to various factors, including climate change, environmental modifications, human and animal movements, urbanization, and socio-economic changes (Barth-Jaeggi and Mäser, 2021). Countries such as France, Italy, Spain, Greece, Portugal, and Turkey have observed the spread of vector-borne diseases and the neglect of leishmaniasis (ECDC, 2022). Additionally, imported cases of leishmaniasis have increased in Italy due to migration and travel from endemic areas outside Europe (Giancetti and Montomoli, 2020).

The epidemiology of leishmaniasis in Europe presents a complex and dynamic picture, with different *Leishmania* spp. and transmission cycles coexisting and interacting. In a recent review, the primary *Leishmania* species identified in Europe were *L. infantum*, accompanied by sporadic

cases of localized transmission of *L. tropica* in Greece and *L. donovani* (*sensu stricto*) in Cyprus (Maia et al., 2023). These species can cause both cutaneous (CL) and visceral (VL) leishmaniasis, with VL primarily caused by *L. infantum* and *L. donovani* (s.s.) while cases of VL caused by *L. tropica* are also reported. (Özbilgin et al., 2023). The distribution of these species varies geographically and temporally, depending on the presence and abundance of suitable sand fly vectors and animal reservoirs (ECDC, 2023).

VL caused by *L. infantum* is the most prevalent form of leishmaniasis in Europe, particularly affecting children and immunocompromised adults (Barth-Jaeggi and Mäser, 2021). The highest incidence rates are reported in the southern Caucasus region, including Georgia and Azerbaijan, as well as the Mediterranean basin countries such as Spain, Italy, Greece, and Portugal (Özbel et al., 2022). The presence of competent sand fly vectors and reservoir hosts, such as dogs, contributes to the transmission of VL in these regions (Maia et al., 2023). Co-infection with HIV poses a significant challenge for VL control, as it increases the risk of clinical disease and relapse, reduces treatment response, and facilitates the spread of the parasite. In the 1990s, HIV/VL coinfection played a crucial role in the re-emergence of VL in southern Europe, and it remains a public health concern, particularly in countries with high HIV prevalence, like Spain and Portugal (Barth-Jaeggi and Mäser, 2021; Kantzanou et al., 2023).

CL caused by *L. infantum* is reported less commonly than VL in Europe. CL caused by *L. infantum* is mainly reported in several countries, including Spain, Italy, France, Greece, Cyprus, Malta, Croatia, Albania, Bosnia-Herzegovina, and neighboring countries in eastern Europe (Maia et al., 2023).

CL caused by *L. major* is endemic in parts of Turkey and Azerbaijan, primarily affecting rural populations living in close contact with rodent reservoirs such as gerbils (*Gerbillus dasyurus*) (Özbel et al., 2022). On the other hand, CL caused by *L. tropica* is endemic in Turkey, primarily affecting urban populations living in poor sanitary conditions (Özbilgin et al., 2019). CL caused by *L. donovani* (s.s.) is a rare and emerging form of leishmaniasis in Europe, reported from Turkey and Cyprus (Kerkuklu and Güran, 2020). It is associated with anthroponotic transmission, i.e. without animal reservoirs.

### 3. The evolving epidemiology of leishmaniasis in Turkey

Leishmaniasis, a disease endemic in Turkey, has experienced significant changes in its epidemiology in recent years. These alterations are influenced by several factors, such as human movement and the presence of various *Leishmania* spp. The primary species involved in leishmaniasis cases in Turkey are *L. infantum*, *L. major*, and *L. tropica* (Özbel et al., 2022). In Turkey, VL caused by *L. infantum* is endemic, with higher incidence rates observed in southeastern regions such as Şanlıurfa and Diyarbakır (Özbel et al., 2022). CL caused by *L. major* is predominantly found in rural areas, particularly in central and eastern regions, where transmission occurs through zoonotic cycles (Özbilgin et al., 2019). CL caused by *L. tropica* is mainly concentrated in southeastern regions, including Şanlıurfa and Adıyaman (Özbilgin et al., 2019).

Leishmaniasis epidemiology in Turkey has been studied extensively. Reported cases have been concentrated in certain provinces, with Şanlıurfa, Adana, Osmaniye, Hatay, Diyarbakır, İçel, and Kahramanmaraş accounting for the majority of cases between 1990 and 2010 (Gurel et al., 2020). However, there has been a shifting pattern, with a decreasing trend observed in Şanlıurfa and increasing trends in other regions. Leishmaniasis transmission in Turkey is predominantly associated with the bite of infected *Phlebotomus* species, particularly *P. papatasi* and *P. sergenti* (Yetişmiş et al., 2022). Changes in the distribution and abundance of sand fly populations have been observed in different regions of Turkey, potentially linked to urbanization, land-use changes, and ecological modifications (Kasap et al., 2019; Touray et al., 2023). These shifts in vector distribution have led to the emergence of

new transmission areas, extending the geographical range of leishmaniasis within the country.

A recent study demonstrated the presence of *Leishmania* infections in sand flies from various regions. Specifically, *L. tropica* was found in sand flies from Antalya, *L. infantum* was detected in sand flies from Kayseri, and *L. major* was identified in sand flies originating from Cyprus (Yetişmiş et al., 2022). These findings offer valuable insights into the distribution and variety of *Leishmania* spp. across various geographical regions. They contribute to enhancing our comprehension of the epidemiology and the associated risks linked with these infections. A comprehensive survey conducted in several Balkan countries emphasized the presence of multiple sand fly species, including potential vectors of *Leishmania* spp., indicating the re-emergence potential of leishmaniasis in the region (Dvorak et al., 2020).

In addition to the vectors of leishmaniasis, the identification of novel reservoir hosts is crucial for understanding the epidemiology of leishmaniasis in Turkey. A recent study investigated rodents and found *Leishmania* infections in 1.12% of the tested animals, involving *L. infantum*, *L. tropica*, and *L. major* (Karakuş et al., 2020). Specifically, *Apodemus* spp. from the western Black Sea region were found to carry *L. major* and *L. infantum* DNA, while *Meriones* sp. and *Gerbillus dasyurus* from the eastern Mediterranean region were identified as carriers of *L. tropica* DNA (Karakuş et al., 2020).

Human activities, including migration, travel, and conflict-related displacement, have also played an important role in the changing epidemiology of leishmaniasis in Turkey (Özbilgin et al., 2020). The movement of individuals from endemic regions to non-endemic areas or across borders can introduce leishmaniasis into new environments, triggering localized outbreaks and establishing new transmission cycles (Lindner et al., 2020). The influx of refugees and internally displaced populations has further contributed to the spread of the disease, as crowded living conditions and inadequate access to healthcare create favorable conditions for leishmaniasis transmission (Ergönül et al., 2020). Notably, there has been a noteworthy shift in the autochthonous transmission of all four species (*L. donovani*, *L. infantum*, *L. major*, and *L. tropica*) responsible for Old World leishmaniasis infections. This was demonstrated in a recent study, which provided evidence of local transmission of these species within the country (Özbilgin et al., 2022).

Additionally, *L. donovani* has been recently identified in Turkey, and both CL and VL cases have been reported with *L. donovani* as the causative agent (Özbilgin et al., 2017). This suggests that the presence of *L. donovani* in Turkey has contributed to the emergence of both CL and VL cases, necessitating further investigation into the epidemiological and clinical aspects associated with *L. donovani* infections. Furthermore, the first case of *Leishmania aethiops*, a species previously unreported in Turkey, has been documented recently (Özbilgin et al., 2020). This finding highlights the expanding range of leishmaniasis-causing species in the country, indicating potential changes in the disease landscape.

Moreover, investigations have revealed the presence of a hybrid strain between *L. infantum* and *L. donovani*. This hybrid strain has been detected not only in the host but also in the vector and reservoir, pointing toward its presence and circulation in Turkey (Tunali and Özbilgin, 2020). The discovery of hybrid strains highlights the dynamic nature of leishmaniasis in the region, showcasing the potential for genetic exchange and the emergence of new strains with altered features.

Climate change, another influential factor, has impacted the epidemiology of leishmaniasis in Turkey (Özbel et al., 2022). Alterations in temperature and rainfall patterns, as well as environmental modifications, can influence the distribution and abundance of sand fly vectors, thereby affecting the transmission dynamics of the disease (Karmaoui et al., 2022). As climate change continues to reshape ecological conditions, regions that were previously unaffected by leishmaniasis may become suitable habitats for sand fly populations, potentially leading to the introduction and establishment of the disease in new areas (Van der Auwera et al., 2022).

These recent findings illuminate the changing landscape of

leishmaniasis in Turkey, where multiple species and hybrid strains are currently in circulation. These evolving epidemiological patterns, combined with the identification of new species, hybrid strains, and reservoir hosts, underscore the dynamic character of leishmaniasis within the country. Therefore, it is crucial to enhance surveillance, understand transmission dynamics, and implement targeted prevention and control strategies to effectively manage disease propagation and safeguard public health.

#### 4. The threat of leishmaniasis and future directions

The changing epidemiology of leishmaniasis in Turkey holds significant implications for Europe and emphasizes the need for comprehensive surveillance and effective prevention strategies. The rise of CL and the presence of *L. tropica* and *L. donovani* in Turkey pose a substantial risk for the emergence of these *Leishmania* species in European countries, particularly in Mediterranean regions with suitable vector populations. The high incidence of human VL caused by *L. infantum* in the southern Caucasus, coupled with the increasing prevalence of CL and the presence of *L. tropica* and *L. donovani* in Turkey, highlights the potential for leishmaniasis caused by these disease agents to spread into Europe. Furthermore, the recent reports of VL caused by *L. tropica*, which is the most prevalent agent of leishmaniasis in Turkey, are another cause for concern (Özbilgin et al., 2023).

This risk is further exacerbated by the expansion of sand fly habitats due to climate change and the increased relocation of infected hosts, particularly dogs. To address these challenges, it is crucial to implement robust surveillance systems that encompass humans, animals, and vectors (Rombola et al., 2021). Improved standardization in *Leishmania* typing, including well-validated standard operating procedures for testing, interpretation, and reporting, is essential to enhance the accuracy and consistency of data. This will enable better monitoring of the changing epidemiology and facilitate early detection of outbreaks (Van der Auwera et al., 2022).

Furthermore, effective prevention and control strategies must be implemented based on the gathered data. Vector control measures, such as targeting sand fly habitats and implementing insecticide-treated bednets, can help reduce the transmission of leishmaniasis (Sasidharan and Saudagar, 2021). In Europe, preventive strategies for domestic animal hosts are also very important, and the preferred preventive measure primarily involves the use of repellents, with vaccines and Leisguard® being considered as secondary options for preventing *L. infantum* infection (Baxarias et al., 2022). Public awareness campaigns, following a One Health approach that considers the interconnectedness of human and animal health, are crucial to promote preventive measures and educate communities about the risks associated with leishmaniasis. The implications of the changing epidemiology in Turkey extend beyond its borders. Given Turkey's geographical location on the main migration routes towards Europe and its proximity to countries already endemic for leishmaniasis, the spread of these diseases from Turkey to neighboring regions is a significant concern. Therefore, close collaboration and information sharing between countries are vital to coordinate surveillance efforts and implement timely interventions.

The shifting epidemiology of leishmaniasis in Turkey stands as a significant exemplar for Europe, emphasizing the potential risks that the continent may encounter in the future. As climate change, human migration, and other contributing factors persistently reshape the dynamics of leishmaniasis, it is imperative for European countries to maintain a state of vigilance and proactively enhance their surveillance and control measures. The experiences and lessons learned from Turkey can inform preparedness strategies, risk assessments, and targeted interventions in Europe to prevent the introduction and re-emergence of leishmaniasis in previously non-endemic regions (Van der Auwera et al., 2022).

## 5. Conclusion

By understanding the complex interplay of vector distribution, human activities, climate change, and population movement, Europe can take proactive steps toward mitigating the risks posed by leishmaniasis. Collaborative efforts among policymakers, public health authorities, and researchers are essential to develop robust surveillance systems, implement effective prevention measures, and ensure early detection and prompt treatment of leishmaniasis cases.

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During the preparation of this work, the authors used ChatGPT, an AI-powered language model, to enhance the clarity and coherence of the content. After utilizing this tool, the authors thoroughly reviewed and edited the content as needed, ensuring its accuracy and relevance. The authors take full responsibility for the content of the publication, maintaining its scientific rigor and integrity.

## CRedit authorship contribution statement

**Varol Tunali:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ahmet Özbilgin:** Conceptualization, Resources, Supervision, Writing – review & editing.

## Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

The datasets generated or analyzed in the present review are available from the corresponding author upon reasonable request. The reviewed articles cited in this review are publicly available through their respective journals.

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