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TECHNICAL REPORT

Surveillance, prevention and control of leishmaniases in the European Union and its neighbouring countries

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Abbreviations

AniL	Animal leishmaniases
CanL	Canine leishmaniases
CL	Cutaneous leishmaniases
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
HIV	Human immunodeficiency virus
HumL	Human leishmaniases
IANPHI	International Association of National Public Health Institutes
ICJ	International Court of Justice
IFAT	Immunofluorescence antibody test
NUTS	Nomenclature of Territorial Units (Eurostat)
PCR	Polymerase chain reaction
RICT	Rapid immunochromatographic tests
UNSCR	United Nations Security Council resolution
VL	Visceral leishmaniases
WHO	World Health Organization
WHO-CP	WHO country profile
WHO-GHDR	WHO Global Health observatory Data Repository
WOAH	World Organisation for Animal Health

Executive summary

This technical report presents the epidemiology of human and animal leishmaniases (HumL and AniL) in the European Union (EU) and its neighbouring countries and describes the surveillance, prevention and control measures implemented. Forty countries in Europe, northern Africa, the Middle East, Turkey and the Caucasus have been included; all countries where leishmaniases are endemic, as well as peripheral non-endemic countries where sand fly vectors of leishmania parasites have been reported. Information was gathered through an extensive, non-systematic review of the scientific and grey literature published between 2009 and 2020, and through questionnaires addressing the public health and veterinary national authorities in the targeted countries. Outputs include (i) a description and analysis of the spatial and temporal dynamics, including presence maps and evidence for emergence, (ii) a description of statutory notification, surveillance and control arrangements, and (iii) a description of levels of access to diagnostic techniques and medicines. This information was collated to provide the basis for recommendations on potential future action to strengthen surveillance, prevention and control of leishmaniases in order to reduce the impact of the disease in Europe and neighbouring countries.

Spatial and temporal dynamics and evidence for emergence

Recent evidence of autochthonous leishmaniases endemicity is available for Albania, Algeria, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Egypt, France, Georgia, Greece, Israel, Italy, Jordan, Kosovo[1], Lebanon, Libya, Malta, Montenegro, Morocco, North Macedonia, Palestine, Portugal, Romania, Serbia, Slovenia, Tunisia, Ukraine, and Turkey.

Leishmania infantum, causing visceral leishmaniasis (VL) and cutaneous leishmaniasis (CL), is present in all these countries, while *Leishmania major* and *Leishmania tropica* causing CL are present only in countries of northern Africa and in Azerbaijan. Meanwhile, *L. donovani sensu stricto* (s.s.) has only been described in certain areas of Cyprus and Turkey.

Common to all regions is a significant increase in disease incidence in the 1980s and 1990s, driven by demographic and societal changes. In northern Africa and the Middle East, the geographical expansion occurred in connection with new agricultural developments and the building of transport infrastructure.

Based on the World Health Organization (WHO)'s Global Health Observatory Data Repository (GHDR), during the period 2005–2008, the estimated median annual incidence per 100 000 population of CL by *L. major* and *L. tropica*, was 65 in Libya, 58 in Tunisia and 34 in Algeria and between three and 11 in Morocco, Israel, Palestine, Jordan and Turkey. In the subsequent 15-year period, reported incidence of CL decreased in Israel and fluctuated greatly in other North African and Middle Eastern countries and Turkey, in association with the extensive flow of war refugees from Afghanistan, Iraq and Syria. By 2017–2020, the highest median annual CL incidence in the area reported to WHO's GHDR was 52 in Tunisia, 51 in Libya, 26 in Algeria and 17 in Morocco. In the affected EU countries, CL incidence increased significantly between the periods 2005–2008 and 2017–2020 (e.g. from 0.01 to 0.27 in France and from 0.03 to 0.40 in Spain).

The WHO-GHDR estimated median annual incidence per 100 000 population of VL by *L. infantum* in 2005–2008 was 4.5 in Georgia, 3.8 in Albania, 1.1 in Tunisia, 0.99 in Malta, 0.52 in Morocco, 0.51 in Spain, and ranged between 0.33 and 0.41 in Montenegro, Greece, North Macedonia, Algeria and Azerbaijan and between 0.12 and 0.24 in Italy, Armenia, Portugal, and Croatia. According to the WHO-GHDR, by the period 2017–2020, the median annual VL incidence had decreased significantly in Georgia (1.20), Albania (0.77), Morocco (0.27), Tunisia (0.22), Algeria (0.09) and Croatia (<0.01). Meanwhile, it increased significantly or marginally in Armenia (0.58), Azerbaijan (0.52), Libya (0.38) and France (0.05). A comparison of the median annual VL incidence of notified cases between 2009–2012 and 2013–2019, available for Greece, France and Bulgaria (data from the national public health authorities) revealed a significant increase in incidence in Greece during the later period ($p=0.01$) and no changes in Bulgaria and France. According to the hospital discharge records in Portugal and Spain, a similar comparison of the median annual incidence of cases hospitalised due to leishmaniasis between these two periods showed a decrease in Portugal from 0.50 to 0.37 ($p=0.05$) and a smaller, insignificant increase in Spain from 0.61 to 0.65 ($p=0.40$). Similarly, VL HDR records from Italy indicated a decrease in incidence from 1.2 in 2011 to 0.5 in 2016. However, analysis of the temporal trend of VL incidence in Spain and Italy revealed significant differences between regions. Discrepancies in the reported incidence between WHO sources and HDR available in some countries highlights the inherent underreporting of leishmaniases and the urgent need to improve surveillance and notification systems.

Countries differed in terms of the age distribution of human VL. Countries with a lower gross domestic product situated in the Caucasus, eastern Europe and northern Africa have a higher incidence of paediatric leishmaniases than western European countries, where adults represent the majority of the cases. Most of these adult cases were patients undergoing immunosuppression therapies for organ transplants, autoimmune diseases and cancer. In addition, adult cases in western European countries included immunocompetent people lacking acquired immunity to the parasite. One

[1] This designation is without prejudice to positions on status, and is in line with UNSCR 1244/1999 and the ICJ Opinion on the Kosovo Declaration of Independence

example of this was an outbreak affecting around 1 000 immunocompetent people on a housing estate in the outskirts of Madrid, Spain, where the outbreak involved hares and wild rabbits, an unusual reservoir host of *L. infantum*. Smaller localised epidemics in the general human population in Italy and Spain have also been reported.

Rural environments are the areas where VL traditionally has a high incidence. However, peri-urban residential environments in southern Europe have also become hotspots for leishmaniases. In Albania, Georgia and northern Africa, there are urban VL transmission cycles associated with dogs, including stray animals. In North Africa and the Middle East, CL by *L. major* predominantly occurs in rural areas and is linked to autochthonous rodent reservoir hosts. Meanwhile, *L. tropica* has established both rural and anthroponotic urban cycles.

Veterinary and public health authorities in Albania, Algeria, Armenia, Austria, Azerbaijan, Cyprus, France, Georgia, Italy, Malta, Montenegro, North Macedonia, Romania, Spain and Turkey indicated in questionnaire responses that leishmaniasis was an emerging disease in their country or in some regions. They reported that the emergence had been driven by insufficient surveillance and control, climate and other environmental changes and movement of infected dogs and humans. Movements of infected dogs and humans was deemed a major risk for the introduction and establishment of *Leishmania* in peripheral non-endemic areas where vectors are present. Leishmaniasis in dogs is extensively underreported and there is evidence that it has spread northwards and is now present at higher altitudinal ranges in Italy and Spain. The disease has also recently been described in countries that were previously *Leishmania*-free, such as Romania. Furthermore, the establishment of *L. tropica* in southern Europe, where vectors are naturally present in many areas, is a serious concern.

Statutory notification, surveillance and control

The notification of human leishmaniases is mandatory in all endemic countries, with the exception of France, Egypt and Serbia. Animal leishmaniases are not notifiable in France, Turkey, Romania, Serbia and Palestine, while information for Morocco, Tunisia, Egypt and Lebanon was unavailable. In most non-endemic countries, including Germany, Austria, Belgium and Hungary, human and/or animal leishmaniases are non-notifiable. Nevertheless, it is a requirement for all countries to report cases of animal leishmaniasis to the World Organisation for Animal Health (WOAH) and cases of human leishmaniasis to the World Health Organization (WHO).

With the exception of Romania and Serbia, where there is no surveillance of HumL, all endemic countries have implemented passive surveillance for HumL and this surveillance is comprehensive (delivered by all health providers) except in Libya and Malta where sentinel schemes are running. Although surveillance of AniL is not performed in as many countries (these countries include Algeria, Armenia, Cyprus, Italy, North Macedonia and Spain), all have comprehensive schemes, except Armenia which relies on a sentinel scheme. In Armenia, Cyprus, Italy, Spain and Ukraine the target animal population for surveillance includes symptomatic and asymptomatic dogs (household, shelter, kennel and stray). Spain also conducts surveillance on wild animals with leishmaniases foci. No information was available on the target population in Algeria and North Macedonia.

Based on questionnaire responses, national control programmes for HumL have been established in 20 out of 26 endemic countries, although no information on these programmes could be found on national governmental web pages. Albania, Cyprus, Jordan, Lebanon, Montenegro and Ukraine do not have a national control programme for HumL. Availability of national control guidelines was confirmed for seven countries. Fewer countries have a specific national control programme for AniL, but the majority of them have adopted a 'One-Health' approach to leishmaniases prevention. HumL control typically involves curbing infection in animal reservoirs, including dogs for *L. infantum*, wild rodents for *L. major* and wild rodents and hyraxes for *L. tropica*. Common prevention and control practices for dogs include the application of preventive topical insecticides and treatments, and euthanasia in sick animals that cannot be treated. Wild reservoirs of AniL are controlled by destroying burrow nesting habitats, removing plant diet sources and poisoning. *L. major* and *L. tropica* are also controlled by spraying insecticide in the domiciliary environment and using insecticide-treated bed-nets. However, only a minority of countries combine all of these control actions and the scale is often limited to outbreak areas and the action only undertaken for short periods.

According to the veterinary and public health authorities, the main challenges to disease control were lack of funds and capacity constraints and, to a lesser extent, the lack of regulation and availability of rodenticides and insecticides.

Diagnosis and treatment

In all countries, diagnosis of clinical leishmaniases relies on clinical examination, epidemiological information and parasite identification by optical microscopy using skin and lymphoid tissue samples for CL and VL, respectively. Parasitological confirmation using the more sensitive polymerase chain reaction (PCR) test is common in western Europe, Israel and Turkey, and has more recently been introduced in some of the less affluent countries. Although PCR is also widely used for HumL surveillance, it is less frequently used for AniL surveillance. Serological assays are cheap and have a high sensitivity for VL diagnosis but are rarely used for CL diagnosis. Among those countries that responded to the questionnaire, diagnostic guidelines were reported as being available in 11 out of 21 for HumL and three out of 26 countries for AniL. All countries employ serological methods for VL diagnosis and only Algeria, Armenia, Georgia and Ukraine do not routinely use PCR tests.

Serological antibody tests include immunofluorescence antibody test (IFAT), enzyme-linked immunosorbent assay (ELISA) and rapid immunochromatographic tests (RICT).

Serological and PCR methods are extensively used by research groups to detect and estimate the prevalence of *Leishmania* infection in randomly selected animals and captured vectors. Infection has been confirmed by PCR in many domestic and wild hosts and sand fly species. The ability of host species to transmit infection to the vector has not been tested in most cases and their epidemiological importance is unknown. PCR prevalence is often >50% in dogs and rodent reservoir hosts, and 0–10% in the majority of sand fly studies. Seroprevalence typically ranges between 5% and 30% in dogs, but is generally lower in cats. It is rare for wild animals to be tested serologically, due to a lack of specific tests. However, prevalence often varies widely within a human or animal population, depending on test sensitivity and specificity and the biological sample used. There is a need to standardise PCR and serological tests for leishmaniasis diagnosis.

Leishmanicidal pentavalent antimonial drugs, such as meglumine antimoniate and sodium stibogluconate, have been the standard treatment for human VL and disseminated CL for decades and this is still the case for canine leishmaniases. Less toxic and more expensive Liposomal amphotericin B, miltefosine and injectable paramomycin replaced antimonial drugs for human treatment more than a decade ago in western Europe and Israel, but only a few years ago in most other countries where they are often used as a second option if antimonials fail as a result of parasite resistance. Among the 23 countries that provided information on VL treatment availability in humans, liposomal amphotericin B is used in 19, meglumine antimoniate in 18 and miltefosine in 11 countries. Four countries were unsure of the treatment used. Human treatments for localised CL include the intralesional application of meglumine antimoniate, paramomycin ointments, cryotherapy, thermotherapy and surgical excision. Canine leishmaniasis treatments included meglumine antimoniate, allopurinol, miltefosine and sodium stibogluconate in 16/17, 10/11, 13/15 and 3/9 countries, respectively.

Conclusions

Leishmaniases remain widespread and underreported in many countries of southern Europe, northern Africa, and the Middle East. There is a need to improve leishmaniasis prevention and control based on robust surveillance in humans, animals and vectors, and to increase public awareness following a 'One-Health' approach. Current leishmaniasis prevention and control measures and access to valid diagnostic methods and effective treatments are insufficient. This could have important disease implications including an increase in incidence in the EU and its neighbouring countries; the spread of *Leishmania spp*. into new areas going unnoticed; increases in treatment failure and the development of resistance to treatments.

1. Background

1.1. General information about leishmaniases and *Leishmania*

Leishmania are protozoan parasites (Kinetoplastida, Trypanosomatidae) of phagocytic cells in humans and animals, transmitted by phlebotomine sand flies (Diptera, Psychodidae). The insects are prevalent at warmer latitudes, including part of the European Union (EU) and its neighbouring countries. Four species are recognised in this area: *L. donovani* complex species including *L. infantum* and *L. donovani* s.s., *L. tropica* and *L. major*, and two major clinical forms: visceral leishmaniasis (VL), a severe condition caused mainly by the *L. donovani* complex species which has a high mortality rate if not treated, and cutaneous leishmaniasis (CL), a more frequent but less severe condition caused by any of the four species [1]. Leishmaniases are considered to be neglected [2,3], underreported diseases and the estimated number of human cases of VL and CL in the World Health Organization (WHO) European Region is 1 100–1,900 and 10 000–17 000 cases per 100 000 population, respectively [1].

The spatial distribution of *Leishmania* spp. varies considerably. *Leishmania infantum* is found in southern European countries; dogs are highly susceptible to infection, making them the most important domestic reservoir of infection [1]. In contrast, *L. major* and *L. tropica* are restricted to northern Africa and in some parts of the Caucasus; their primary reservoir hosts include several species of wild rodents and hyraxes. Humans are also natural reservoirs of *L. tropica* and this species has anthroponotic transmission cycles without the intervention of animals. An anthroponotic *L. tropica* cycle was present in Crete until the mid-twentieth century and some cases were reported in the first decade of the twenty-first century, suggesting the disease had re-emerged on the island [4]. Humans are also the principal reservoir of *L. donovani s.s.* This is the least common species in the study area, so far described only in Turkey and Cyprus [5,6].

Susceptibility to *Leishmania* strongly depends on the host's immune response, and cell-mediated immunity is essential to prevent disease development. Parasitological cure is rare and the prevalence of subclinical infection in endemic areas, particularly in rural and peri-urban environments, is usually high [1]. Malnutrition in childhood and immunodeficiency syndromes from human immunodeficiency virus (HIV) infection and immunosuppressive treatments for autoimmune conditions and organ transplantation [7-10] are major risk factors for VL by *L. infantum.* However, occasionally VL may also take on epidemic proportions in immunocompetent adults with no acquired immunity to the parasite [11]. Northern Africa, the Middle East and Central Asia bear the brunt of leishmaniases in the WHO European Region and tens of thousands of children and adults are affected by CL caused by *L. major* and *L. tropica* [12]. The control of leishmaniases in humans is hampered by the lack of effective vaccines although intradermal inoculation of live parasites to induce active immunity was a common practice in some highly endemic CL areas until recently [13]. In contrast, several vaccines have been commercialised to prevent CanL by *L. infantum,* including two in the EU but their efficacy is only partial and they do not prevent infection [14]. In fact, one of them was recently withdrawn from the market.

Leishmania strains can be separated on the basis of their isoenzyme profiles, and viscerotropic and dermotropic *L. infantum* variants typically group as separate zymodemes. While dogs are the domestic reservoir for *L. infantum*, some dermotropic zymodemes are not common in dogs, suggesting that *L. infantum* may also have an anthroponotic cycle which is not dependent on dogs [15].

Diagnosis of leishmaniases in humans and animals relies mostly on the detection of characteristic clinical signs and parasitological confirmation of infection by microscopy in skin samples of CL patients and lymphoid tissue samples (bone marrow, lymph node, spleen) of VL patients. Polymerase chain reaction (PCR) and serological techniques, including immunofluorescence antibody test (IFAT), enzyme-linked immunosorbent assay (ELISA), rapid immunochromatographic tests (RICT), direct agglutination test and western blot, are now also available at universities and public health laboratories. PCR is a very sensitive technique for both CL and VL diagnosis. In contrast, serological tests are rarely used to detect CL infections as these infections do not stimulate a strong antibody response [16].

Due to its severity, human VL cases are typically treated in hospitals and in general, a larger proportion of cases are notified than CL cases, since CL cases often experience a few, small, painless and self-healing lesions and do not seek hospital treatment. Alvar et al. [17] considered underreporting to be mild when 1.2–1.8-fold for VL and 2.8–4.6 for CL, and moderate when 2–4-fold for VL and 5–10-fold for CL.

1.2. Scope and objectives of the study

The review covers human and animal leishmaniases caused by *L. infantum*, *L. major*, *L. tropica* and *L. donovani s.s.* between the years 2009 and 2020 in the EU Member States and neighbouring countries (the EU enlargement countries and the EU Neighbourhood Policy countries) where leishmaniases are endemic. It also covers those countries with confirmed or suspected presence of sand fly vectors, according to the literature and the VectorNet sand flies distribution maps [18]. The following countries were included: Albania, Algeria, Armenia, Austria, Azerbaijan, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czechia, Egypt, France, Georgia, Germany, Greece, Hungary, Israel, Italy, Jordan, Kosovo, Lebanon, Libya, Luxembourg, Malta, Moldova, Montenegro, Morocco, North Macedonia, Palestine, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Switzerland, Syria, Tunisia, Turkey and Ukraine.

Several studies indicate that leishmaniases have been emerging in the EU and neighbouring countries over the last decade in association with human-induced environmental changes [11,14], although the scale of this has not been investigated.

The objectives of the study were to i) describe the epidemiology of leishmaniasis in the EU and its neighbouring countries and assess its potential emergence; ii) describe the surveillance, prevention and control measures in place, including the availability of diagnostic tests and treatments, and iii) identify gaps in the surveillance, prevention and control of human and animal leishmaniasis.

2. Methods

Data were collected through a literature review and a questionnaire survey.

2.1. Literature review

The literature review searched for information published between January 2009 and July 2020 that included scientific articles selected from the SCOPUS database (https://www.scopus.com). The comprehensive search included national repositories of completed PhD and MSc theses, and national and international governmental and non-governmental human and animal health organisations websites. Documents in English, Spanish, Portuguese, French, Italian, Turkish, Hebrew and Russian were reviewed. In addition, a search for grey literature was performed.

2.1.1 Scientific articles

Two separate Boolean search strategies were performed in July 2020 to select articles covering aspects of leishmaniasis epidemiology, diagnosis, treatment and control, and those articles specifically related to *Leishmania* infection rates in sand flies. Details of these strategies are provided in Annex 1 (available as a downloadable file)[2]. Briefly, Strategy 1 included the term 'Leishman*' (*placeholder for one or more words) in the title OR in the abstract, AND one or more of nine *Leishmania* species, AND one or more datatypes related to epidemiology, diagnosis, treatment and control, AND one or more names of countries or territories in the study area, in any of the article fields. Strategy 2 searched for articles with the terms 'sandfl*' OR 'sand fl*' OR 'phlebotom*', AND 'Leishman*', AND 'infection rate' OR 'infect* OR detect* OR characteriz* OR typing OR identification', AND one or more names of countries or territories in the study area, title, abstract or keywords.

Given the high number of papers retrieved from the search, the papers were divided into two groups and titles/abstracts screened by two independent reviewers for each group. One additional reviewer (fifth reviewer) ensured the consistency between the two groups. The screening was done based on inclusion criteria aiming to capture articles describing leishmaniases surveillance, prevention, control, diagnostic test and treatment availability in humans and animals, and sand fly infection rates in the study area. Disagreements between reviewers were resolved by the fifth reviewer.

2.1.2 PhD and MSc thesis

The search for PhD and MSc theses was executed in the global Directory of Open Access Repositories (OpenDOAR), the national thesis repositories, the 'Open Grey' web page and the DART Europe E-Theses Portal, following the step-by-step search protocol in Annex 2 (available as a downloadable file). Theses incorporating the keywords 'Leishmania', 'leishmaniosis' and 'leishmaniases' were preselected and, based on an analysis of the title and abstract, those relevant to the project were selected. All five reviewers participated in this task.

2.1.3 Documents and data from national human and animal health institutions

Web pages of national ministries for human and animal health and the public health institutes of every country included in the project were searched following the protocols described in Annex 3 (available as a downloadable file). The list of the sites to be searched was derived from website directories available on the websites of WHO, the European Food Safety Authority (EFSA) and the International Association of National Public Health Institutes (IANPHI). The keywords 'Leishmania', 'leishmaniosis' and 'leishmaniases' were used to locate relevant documents, and Google Translate was used to screen web pages available only in languages unfamiliar to the research team.

In addition, requests were made to the national focal points of ECDC (whom are representatives of the public health institutes in the EU/EEA), to provide data on hospitalised leishmaniasis cases from their centralised hospital discharge database, also known as Minimum Basic Data Set (MBDS), and data on reported leishmaniasis cases from the national notification systems of the countries for the period 2009–2020.

2.1.4 Documents and data from international human and animal health organisations

The web pages of WHO, ECDC, the Food and Agriculture Organization of the United Nations (FAO) and the World Bank were searched for human health, and OIE-WAHIS (World Animal Health Information System) and EFSA for animal health, using the following key words 'Leishmania', 'leishmaniases', 'sand flies', and 'sandflies'. The complete

[2] Tables & annexes available as downloadable files at the following link: https://www.ecdc.europa.eu/en/publications-data/tables-annexes-surveillance-prevention-control-leishmaniases-report

search protocol is presented in Annex 4 (available as a downloadable file). WHO documents included the latest leishmaniases country profiles summarising the epidemiological situation, control and surveillance activities and availability of diagnosis, treatment and medicines for some of the study countries and the WHO Global Health Observatory data repository (WHO-GHDR).

2.1.5 Extraction and consolidation of document-level data

Data from the articles and documents that passed the screening stage were extracted by the reviewers and gathered in a Microsoft® Excel data extraction sheet. The data collected were individual-level observations where available (e.g. the number of infected and non-infected individuals) and summary statistics including proportions, means and percentiles. Qualitative data included relevant primary parameters related to hosts (gender, age, etc.), geographical area (coordinates and names of places), diagnostic sample type and tools, treatments and surveillance, control and prevention strategies.

2.1.6 Data analysis and mapping

Frequency distributions were assessed and described using summary statistics, including the mean and standard errors for normally distributed data and median and percentiles for non-normally distributed, numerical variables, and frequencies for categorical variables. Prevalence of *Leishmania* spp. infections/disease was defined as the percentage of infections/individuals with the disease at a particular time. The annual cumulative incidence rate per 100 000 people of notified cases (hereafter incidence) was calculated as the number of notified cases in a year divided by the population census and multiplied by 100 000. Country censuses were obtained from the Spanish financial journal 'Expansion' (https://www.expansion.com/). Median incidences were calculated for grouped yearly periods, and the non-parametric Kruskal-Wallis test was used to compare median incidences across year groups. Significance was considered for $p<0.05$ for a double-sided test. All analyses were performed using the statistical programme R [19].

The geographical coordinates of sites where *Leishmania* spp. and leishmaniases cases were reported were obtained from the articles, where provided, and otherwise they were obtained from ECDC's web application viewer [20]. The geographical information system ArcGIS [21] was used to elaborate polygon maps using spatial administrative units NUTS3 (Nomenclature of territorial units level 3), GAUL 1 (Global Administrative Unit Layer) and GAUL 2, depending on the country's administrative sub-division level. They represent all cases reported in the literature for a particular administrative sub-division, excluding cases explicitly described as imported (from another country or region). Therefore maps do not necessarily represent areas where autochthonous transmission occurred as this could not be established in most instances.

2.2 Questionnaire surveys

Separate questionnaires were developed on animal and human leishmaniases.

2.2.1 Definitions and specifications

Animal leishmaniasis referred to infections in domestic or wildlife hosts caused by *L. infantum* only. Human leishmaniases referred to infections by *L. infantum*, *L. major*, *L. tropica* and *L. donovani*. Surveillance was defined as the systematic and continuous gathering, management, analysis, interpretation and reporting of infection/disease data to conduct health actions. Surveillance was defined as comprehensive when it involved all official and private public health and veterinary services in the reporting country. Infections were defined as autochthonous in a particular country if they followed natural *Leishmania* transmission within the country. Mandatory notification referred to the obligation by law to report cases of infection to governmental authorities. Leishmaniasis was deemed to be an emerging disease if infection/disease was identified for the first time in a geographical area or where a recent increase in incidence was reported in an already endemic area due to higher vector-borne transmission.

The challenges for prevention and control and the drivers for emergence were captured through numerical questions ranking the relative importance from 0 (not important) to 3 (very important).

2.2.2 Target survey population and questionnaire administration

The two questionnaires were sent to the national focal points of ECDC and WHO and the national focal points of EFSA and WOAH who are official representatives of the national public health authorities and the national veterinary authorities, respectively. The national authorities from all countries included in this study, except Switzerland, were contacted.

The EU survey tool of the European Commission was used to administer the questionnaire online. ECDC sent the two questionnaires to all national focal points on 11 September 2020 and a reminder on 28 September 2020 to those who had not completed the questionnaires following the first request.

Responses to the questionnaires were exported from the EU survey tool into Microsoft® Excel.

3. Results

3.1 General results

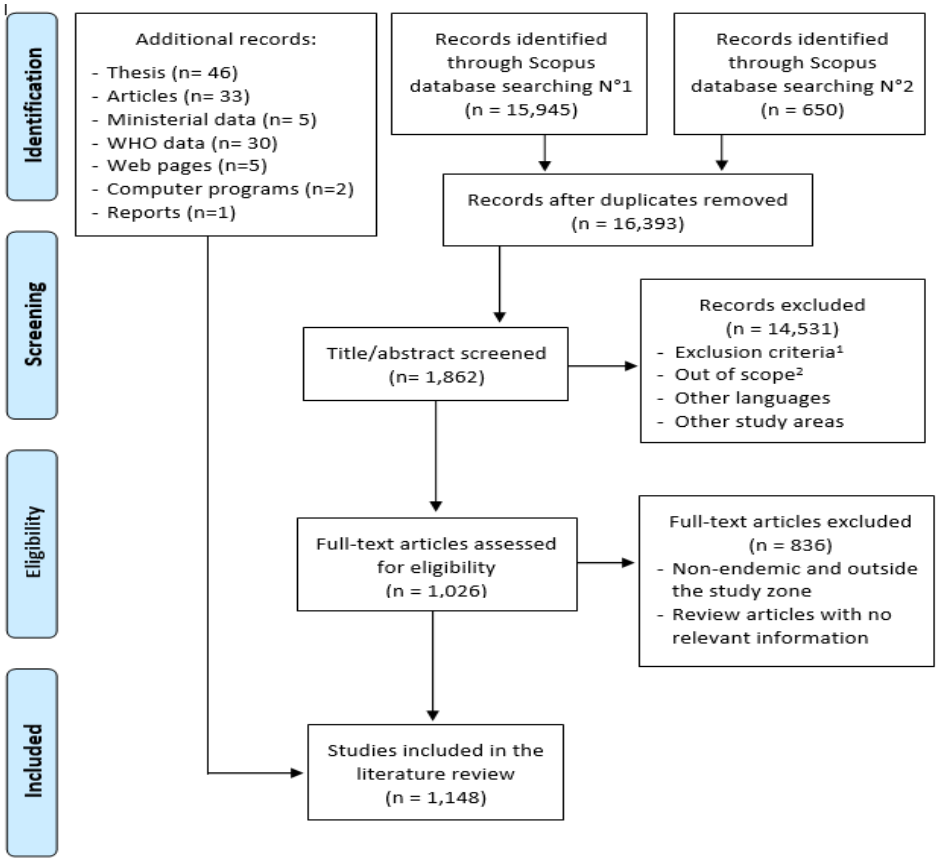
3.1.1 Literature search

The number of articles retrieved from SCOPUS following string searches 1 (leishmaniases epidemiology, diagnosis, treatment and control) and 2 (sand fly infection rates), were 15 945 and 650, respectively (Figure 1). After removing duplicates, there were 16 393 articles, 1 862 of which were selected following screening of title and abstract. After reading the full text articles, 1 026 articles were kept for data extraction.

In addition, 122 additional records (e.g. thesis, WHO data, web pages) were identified and included in the study.

Among the selected articles, 1 083 articles provided geographical information of *Leishmania* spp. and/or sand fly vectors used for preparing maps.

Figure 1. PRISMA flow chart showing the results of the search strategy to select studies to be included in the review



[1] *Exclusion criteria: studies of molecular or biochemical characterisation of Leishmania spp. in vitro drug susceptibility and in vivo laboratory studies.*

[2] *Epidemiology, country surveillance activities, control, diagnostic methods, treatment, opinion on drivers for emergency and impact of leishmaniasis.*

3.1.2 Data provided by national and international health institutions

The annual frequency of notified human leishmaniasis cases in study countries were obtained from four main sources: WHO Country Profiles, including those up to 2010 published by Alvar et al. [17] and later ones for Albania, Armenia, Azerbaijan, Georgia Greece, Italy, Israel, Spain and Turkey (published and unpublished data provided by WHO); WHO GHDR; the national notification systems from Bulgaria, France, Greece and Malta and the centralised hospital discharge database from Spain, Portugal and Italy. Similarly, the annual frequency of notified animal leishmaniasis cases in study countries were obtained from the WOAH website.

3.1.3 Questionnaire responses and geographical distribution of responding countries

ECDC received replies from 27/40 (70%) countries for the animal leishmaniases questionnaire, and from 24/40 (60%) countries for the human leishmaniases questionnaire. Nineteen countries (48%) replied to both questionnaires [22]. All respondents were offered the chance to review the interpretation of the results.

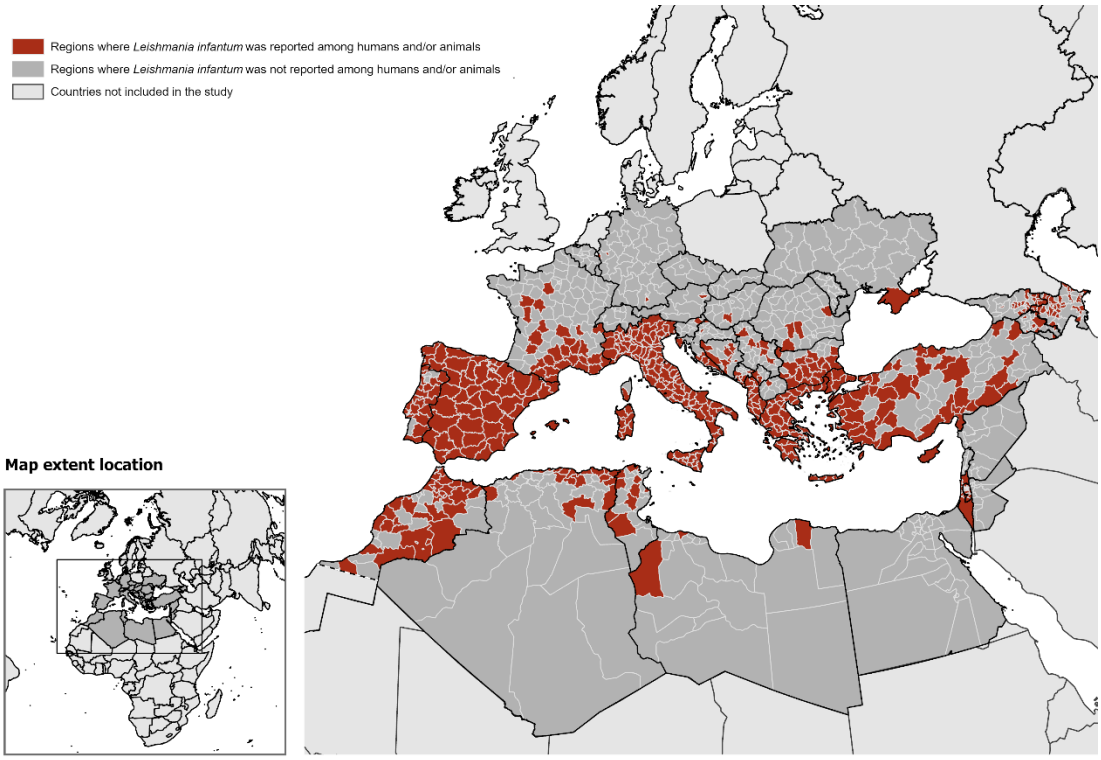
3.2 Status of leishmaniases in the EU and its neighbouring countries

3.2.1 Status of leishmaniases in Europe

General epidemiological features

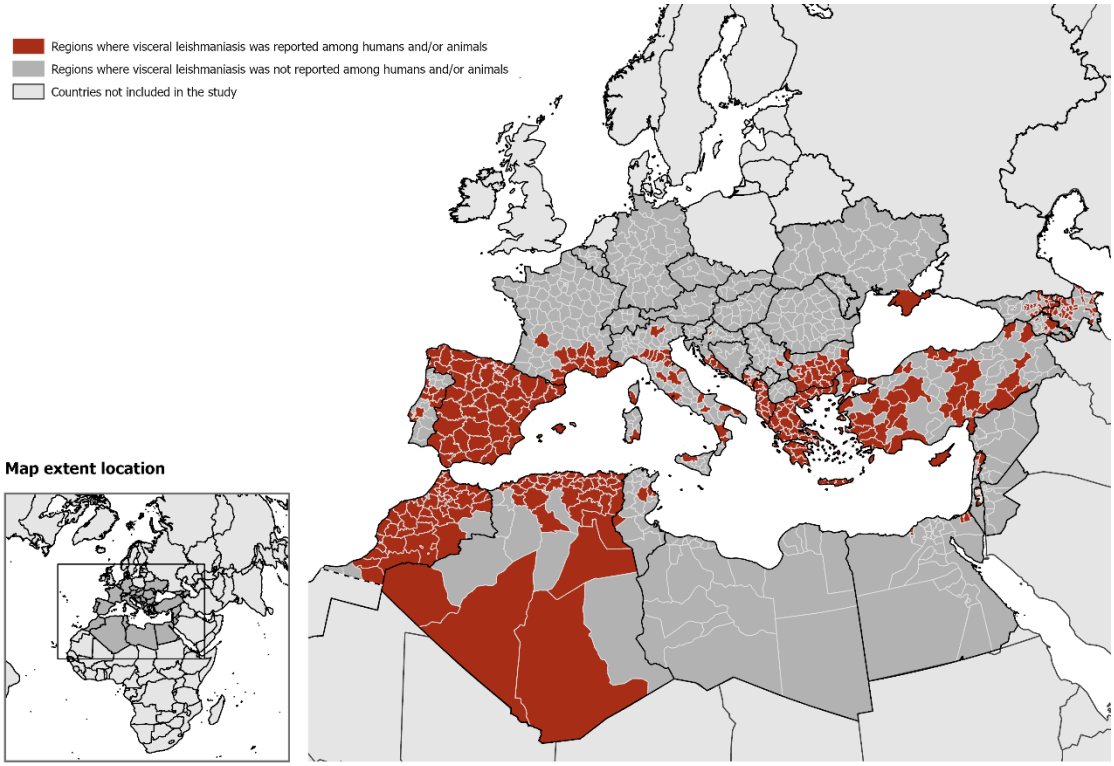
Leishmania infantum is the only autochthonous *Leishmania* species in Europe, causing both VL and CL in humans and animals (Figures 2, 3, 4,5 and 6). Cutaneous leishmaniasis by *L. tropica* was common in Crete during the first half of the twentieth century and a few sporadic cases were detected in the early 2000s, suggesting a relapse of old infection in those affected or a risk of reactivation of old foci [23]. Other cases have been reported from the Ionian Islands. Recently, *L. tropica* DNA was detected in one *P. neglectus* sand fly from Kosovo[3] [24].

Figure 2. Geographical distribution of reported human and/or animal cases of leishmaniasis due to *Leishmania infantum*, European Union and neighbouring countries, 2009–2020



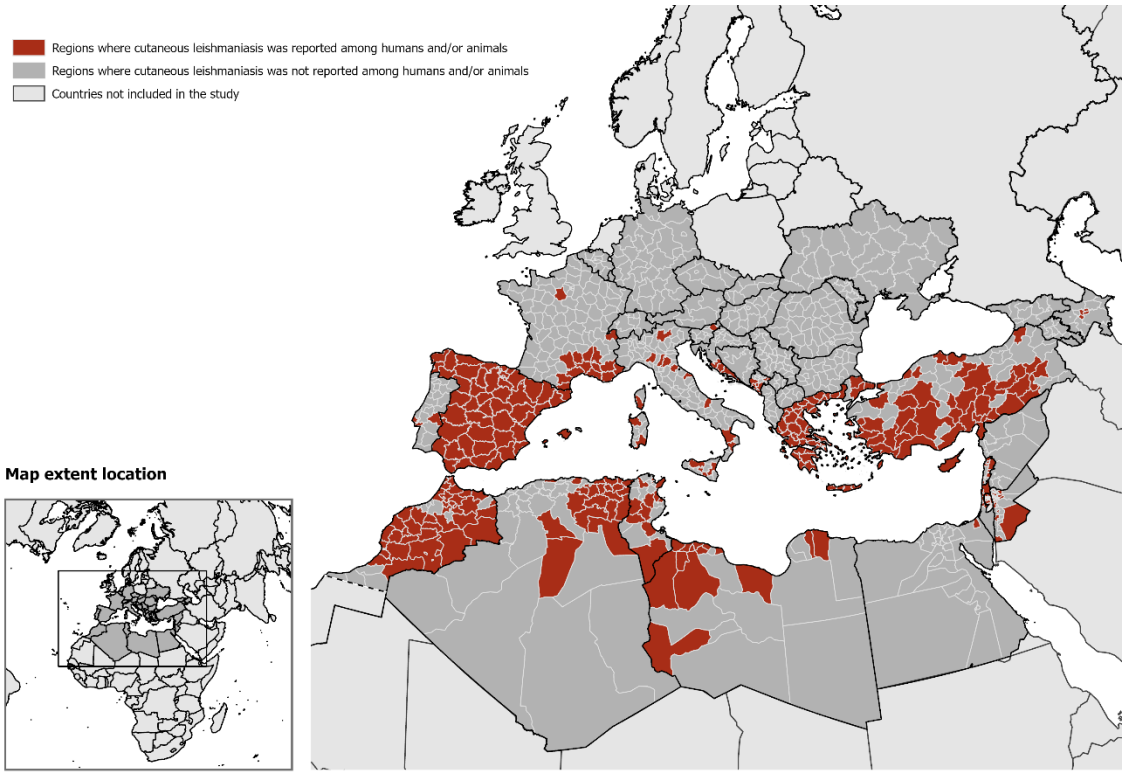
[3] This designation is without prejudice to positions on status, and is in line with UNSCR 1244/1999 and the ICJ Opinion on the Kosovo Declaration of Independence.

Figure 3. Geographical distribution of reported human and/or animal cases of visceral leishmaniasis, European Union and neighbouring countries, 2009–2020



Administrative boundaries: © EuroGeographics © UN–FAO © WHO
The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union.

Figure 4. Geographical distribution of reported human and/or animal cases of cutaneous leishmaniasis, European Union and neighbouring countries, 2009–2020



Administrative boundaries: © EuroGeographics © UN–FAO © WHO
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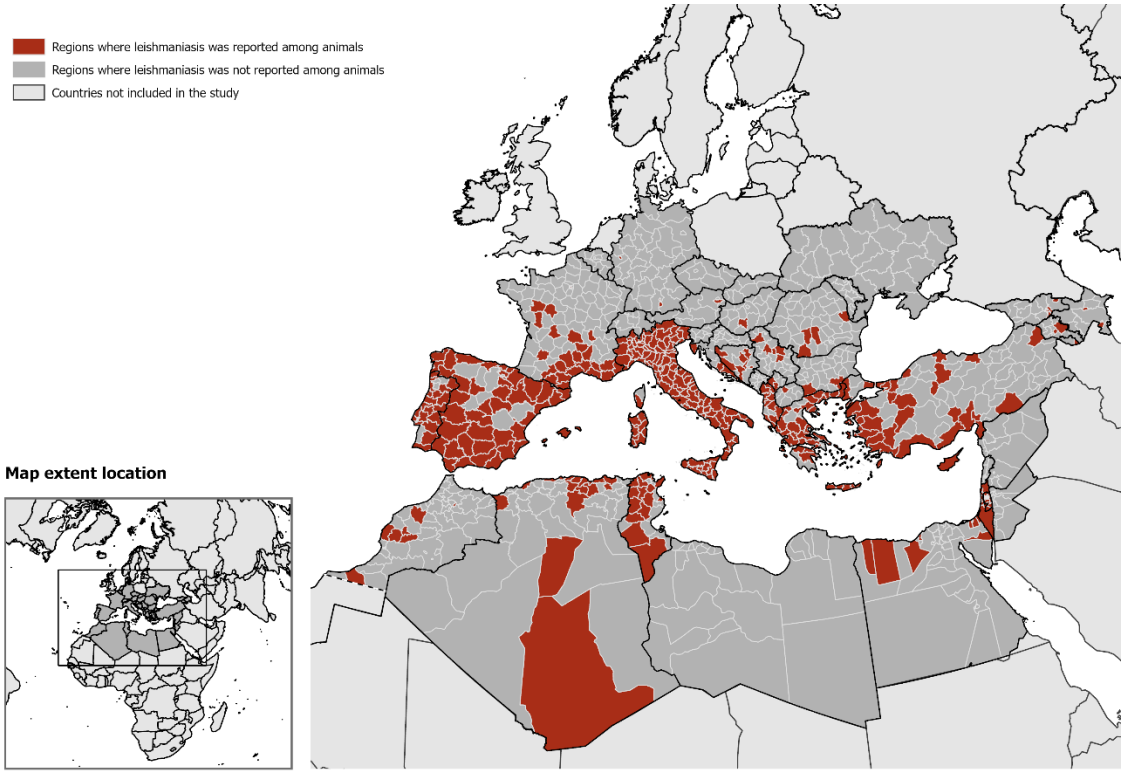
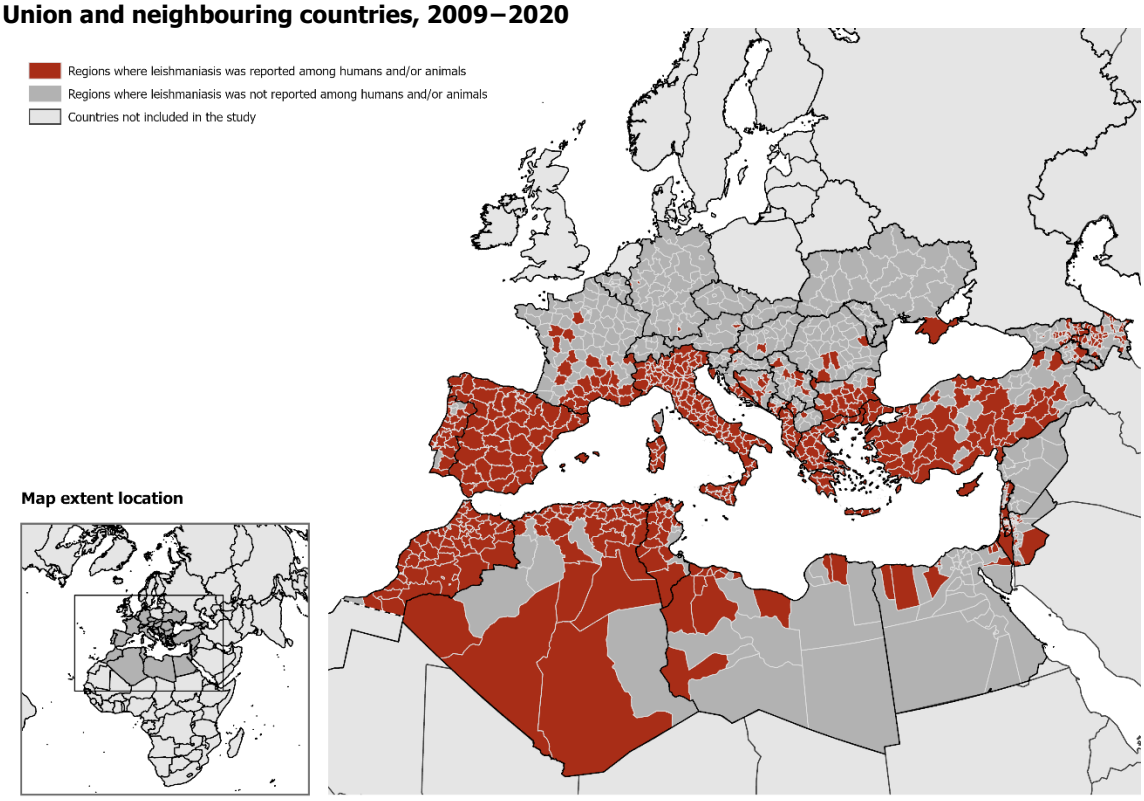
Figure 5. Geographical distribution of reported animal leishmaniasis cases, European Union and neighbouring countries, 2009–2020



Administrative boundaries: © EuroGeographics © UN–FAO © WHO
The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union.

Figure 6. Geographical distribution of reported human and/or animal leishmaniasis cases, European Union and neighbouring countries, 2009–2020



Administrative boundaries: © EuroGeographics © UN–FAO © WHO
The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union.

Most *L. infantum* endemic areas in Europe are situated south of latitude 45, in regions where the vector is present [25]. No sand flies have been reported from Scandinavia, the Baltic countries, the Netherlands or the British Isles. Moderately and highly endemic countries include Albania, Bulgaria, Croatia, Cyprus, France, Greece, Italy, Malta, North Macedonia, Portugal and Spain. Countries with low endemicity, where infections in humans and/or animals have been reported in low numbers, are Bosnia and Herzegovina, Kosovo, Montenegro, Romania and Serbia. Countries with no reported sustained autochthonous transmission, but where vectors were identified and/or sporadic *Leishmania* infections in animals and/or humans were reported include Austria, Belgium, Czechia, Germany, Hungary, Slovenia, Slovakia and Switzerland [26-28].

Europe has a wide range of confirmed and suspected sand fly vectors of *L. infantum*. Broadly speaking, *Phlebotomus perniciosus (P. perniciosus)* and *P. ariasi* are most abundant in western Europe. *Phlebotomus perniciosus* is the main *L. infantum* vector in Italy, Malta and many areas of the Balkans. Its eastern and northern limits are the Crimean Peninsula, western Germany and southern Switzerland, respectively. South-eastern France and Italy represent the western limit for *P. perfiliewi* and *P. neglectus*, respectively. Their distribution reaches Hungary in the north (*P. neglectus* is also found in areas of southern Germany and Switzerland) and they are widespread in eastern Mediterranean countries. *Phlebotomus tobbi* is also present on the Balkan Peninsula. *Phlebotomus mascittii* is the species displaying the greatest longitudinal dispersion in Europe. *Phlebotomus alexandrii* is reported at low density on the Iberian Peninsula and in Greece, and *P. langeroni* and *P. longicuspis* have been sporadically reported in Spain. In addition, *P. papatasi* and *P. sergenti* vectors of *L. major* and *L. tropica* are found in all European Mediterranean countries and *P. similis*, a sister species of *P. sergenti*, has been implicated as a potential vector of *L. tropica* in Crete [29].

European countries differ in terms of the risk factors for leishmaniases. In the Eastern regions of Europe leishmaniases primarily affect children and are particularly associated with poorer living conditions [30-32]. Leishmania-HIV coinfections are more common in western Europe than in eastern Europe [33,34]. Among hospitalised patients with leishmaniasis as a first diagnosis between 1997 and 2011 in Spain, HIV positives represented 36% of patients and children 0−15 years represented 24% of patients [35]. However, during a community outbreak in a recently developed residential area in Madrid during the period 2009−2012, immunocompetent adults represented 96% of the VL and CL cases [36]. The outbreak in Madrid exemplifies the switch in *L. infantum* susceptibility in western Europe, with immunocompetent adults now representing the majority of cases [32] (unpublished data). It is also an example of recent urban planning policy in southern European cities giving rise to potential risks associated with human intervention in sand fly vector environments. Peri-urban residential areas have become vector and *L. infantum* hotspots in southern European countries [37-41].

Movements of people and dogs are important factors for parasite dissemination in Europe [11,42,43]. Such movements are the origin of clinical cases in humans and dogs in non-endemic countries [44-50]. Based on the results of stochastic mathematical models, the mean probability of:

- a dog from a non-endemic area acquiring infection during a trip to an endemic area when no mitigation measures are implemented is estimated to be 8%;
- an imported dog from an endemic area being infected range from 7% to 18%;
- infection becoming established in a dog population in a non-endemic area where competent sand flies exist following the introduction of one infected dog ranges between 47% and 72%, depending on vector density, and is considered very high.

Application of topical insecticides to the non-infected travelling dog reduced the risk of infection by 99.6% [51].

Awareness of the need to assess for *L. tropica* infection among refugees and migrants from the Middle East and North Africa is important in order to mitigate the risk of this species becoming established in areas of southern Europe where *P. sergenti* is widely distributed [11,52].

According to the questionnaire [22], most countries consider leishmaniases as an emergent disease in Europe, driven by the above-mentioned risk factors, climate change and insufficient surveillance and control. Lack of dedicated resources is considered to be the most important control challenge.

Europe has extensive facilities for diagnosing and treating human and animal leishmaniases. Based on the literature review and the answers to the questionnaire, all countries use a variety of serological tests (particularly ELISA, IFAT and RICT) and PCR methods to detect infection, as well as traditional microscopy-based methods. PCR is replacing microscopy in routine leishmaniasis diagnosis in countries with higher resources [53]. However, only a minority of countries have diagnostic guidelines for animal leishmaniases and not many more have diagnostic guidelines for humans. Available treatments for humans, provided free of charge in the public sector, include liposomal amphotericin B (recently and as a second option in less well-resourced countries) and meglumine antimoniate. Two thirds of countries also use miltefosine and just over half of the countries have treatment guidelines [22]. Other treatments used for VL include fluconazole and pentamidine.

Case fatality rates ranged between 1−8% [32] (unpublished data). Human CL treatments include topical paramomycin, intralesional sodium stibogluconate, cryotherapy, thermotherapy, photodynamic treatments and surgical excision [22,33]. Meglumine antimoniate combined with the leishmaniastatic allopurinol is the standard treatment for visceral CanL. No treatment is associated with parasitological cure and allopurinol may have to be continued for life to prevent relapses [54]. Domperidone, an immunomodulatory drug is commonly used [22], though questions have been raised about its benefits versus its potential side-effects [55].

Status of leishmaniases in European countries where autochthonous infections are not or rarely occurring

Status of leishmaniases in Austria
Leishmaniases are not notifiable and no surveillance or control programmes exist. Imported clinical and subclinical infections among civilians acquiring the infection in the Mediterranean area, Latin America, the Middle East and Asia [54,56-58] and in military personnel deployed in Syria, Kosovo and Bosnia and Herzegovina have been reported [45,59]. Infections by *L. donovani* complex, *L. tropica* and *L. guyanensis* were reported.

There is no information in the WHO-GHDR dataset for Austria [32].

There is a report of one asymptomatic dog and one *P. mascittii* sand fly infected with *L. infantum* on a farm in eastern Austria [60].

Status of leishmaniases in Belgium
Leishmaniases are not mandatorily notifiable. The country has passive surveillance of imported VL and CL cases. As there is no sustained autochthonous vector-borne transmission, no control programmes exist [61]. According to the WHO-GHDR dataset, there were 17 imported cases of VL and 100 imported cases of CL between 2013 and 2020 (Table 1)[4] [32].

Status of leishmaniases in Czechia
Leishmaniases are mandatorily notifiable but Czechia does not otherwise implement specific surveillance and control schemes [22]. Between 2009 and 2019, notification of leishmaniasis was mandatory only in domestic animals, though reported as absent [62]. The WHO-GHDR holds no information on leishmaniasis cases in Czechia [32]. Surveys have failed to find vectors in Czechia; however, the vertical transmission of *L. infantum* in dogs over several generations has been reported, with the first bitch presumably becoming infected following a trip to Italy [63].

Status of leishmaniases in Germany
Notification is not mandatory and there is no surveillance or control programme in place. Although not considered a *Leishmania* spp. endemic country, Naucke et al. [64] reported that by 2008, 11 cases had been reported in Germany among humans, dogs, cats and horses, for which an autochthonous origin was confirmed or deemed highly likely. Moreover, there is documented vertical transmission over three generations of dogs, from a bitch that had possibly become infected through sexual transmission [65]. Possible *Leishmania* transmission through dog bite wounds has also been reported [66]. There have been no similar cases or proven cases of autochthonous transmission to date.

Numerous imported human VL and CL cases from various parts of the world have been described [67-73]. *Leishmania* spp. detected in imported cases were *L. infantum, L. major, L. tropica, L. braziliensis, L. mexicana, and L. aethiopica*. According to the WHO-GHDR dataset, there were no cases of VL and 10 cases of CL between 2013 and 2016 (Table 1) [32].

Similarly, available data indicate that the majority of the canine *L. infantum* infections have been diagnosed in dogs imported from various endemic regions or with travel history to countries in the southern part of the European Union (mostly Spain, Portugal, Greece and Italy).

Status of leishmaniases in Hungary
Animal and human leishmaniases are not notifiable in Hungary. There are no specific national surveillance and control programmes. Autochthonous HumL cases have not been described, except for a single case of VL in a young child in the 1940s [74]. The WHO-GHDR dataset reports zero imported VL and CL cases during the period 2013–2016 (Table 1) [32].

Clinical CanL by *L. infantum* was reported in two dogs with no travel history at a kennel in the south-west county of Tolna, and 30% of the dogs in the kennel were IFAT seropositive (Figures 2 and 5) [75]. Farkas et al. [26] describes two of 725 IFAT-positive dogs from six counties and none had travelled abroad.

Status of leishmaniases in Luxembourg
No information on leishmaniasis among humans and animals could be retrieved for Luxembourg. However, it is expected that there is no sustained autochthonous vector-borne transmission in the country.

In Luxembourg, the disease in humans is not notifiable, there is no surveillance and specific control measure in place for human leishmaniasis [22].

[4] All tables are available in a downloadable file at the following link: https://www.ecdc.europa.eu/en/publications-data/tables-annexes-surveillance-prevention-control-leishmaniases-report

Status of leishmaniases in Slovakia
One CL case caused by *L. panamensis* has been reported, imported from the Americas [76]. No data are available for Slovakia in the WHO-GHDR dataset [32].

Status of leishmaniases in Slovenia
Human and animal leishmaniases are notifiable and there is a surveillance programme for HumL; no autochthonous HumL cases have been reported in Slovenia. A case of CL was reported in a child who had lived in Croatia [77]. According to the WHO-GHDR dataset, there was one autochthonous and one imported CL case and two imported VL cases during the period 2017–2020 (Table 1) [32].

The first case of probable autochthonous CanL was recently reported in Slovenia, close to the border with Croatia (Figure 5) [78]. Two surveys among veterinary clinicians in Slovenia revealed the occurrence of a few cases, presumably in dogs that had acquired infection abroad [78,79]. In general, most veterinarians had a good background knowledge of CanL and informed dog owners of the risk to dogs (and subsequently humans) exposed to the disease [78].

Status of leishmaniases in Switzerland
There are reports of imported human VL, CL and mucocutaneous leishmaniases, acquired in Europe, the Middle East, Africa, Central and South America [80-83]. The species involved were *L. infantum*, *L. major*, *L. tropica*, *L. aethiopica*, *L. donovani*, *L. panamensis*, *L. mexicana*, *L. braziliensis*, *L. peruviana*, *L. guyanensis* and *L. naiffi*. No leishmaniasis information is available on Switzerland in the WHO-GHDR dataset [32].

Between 2009 and 2019, one autochthonous animal case (in a horse) was detected in 2015 [62] and a possible autochthonous case of cutaneous leishmaniasis was reported in a Brown Swiss cow, caused by a species with a strong similarity to *L. siamensis* [84]. This species has not been formally named and described and therefore is not taxonomically valid [85]. In fact, it was recently demonstrated that most of the '*L. siamensis*' parasites appear to be identical to *L. martiniquensis* [85]. Between 2009 and 2019, several imported canine, feline and equine leishmaniases cases were reported [86-89].

Status of leishmaniases in European countries with low endemicity

Status of leishmaniases in Bosnia and Herzegovina
Leishmaniases are notifiable, but otherwise there are no specific surveillance and control schemes in place [22]. Between 2009 and 2019, five human cases were reported: one in 2010, 2013 and 2018, and two cases in 2014 [62]. According to the WHO-GHDR dataset, there were two autochthonous VL cases during the period 2013–2016, none between 2017 and 2020, and one CL case between 2005 and 2008 (Table 1) [32]. In 2013, 8% of Austrian soldiers returning from Bosnia Herzegovina and other Balkan countries tested positive for antibodies using ELISA (enzyme-linked immunosorbent assay) techniques [59].

In 2017, *Leishmania infantum* DNA from a dog showing clinical signs from the south of the country was amplified by PCR [90]. In a recent CanL prevalence study, IFAT and blood PCR prevalence were 17% and 3%, respectively, and positive animals came from 10 geographical areas (Figures 2 and 5) [91].

Status of leishmaniases in Kosovo
There are no reports of human leishmaniases in Kosovo other than Austrian soldiers testing positive for antibodies after being stationed in Kosovo and other Balkan countries [59].

Evidence of CanL in Kosovo was first provided by Lazri et al. [92] who reported 1.6% (2/121) IFAT seroprevalence. Recently, Xhekaj et al. [93] described 18% ELISA seroprevalence in 125 dogs in the municipalities of Prizren, Gjakova, Rahovec and Deçan (Figures 2 and 5). Three of 23 seropositive dogs presented typical clinical signs of CanL.

Leishmania tropica DNA was detected by PCR in one *P. neglectus* female from Zhur in the southern province of Prizremski, a few kilometres from Albania [24].

Status of leishmaniases in Montenegro
Human leishmaniases are notifiable, but otherwise no specific surveillance and control is implemented [22]. Alvar et al. [17] reported an average of three annual cases between 2004 and 2008, with underreporting considered mild. The country registered 65 VL and one CL in humans between 1993 and 2013 [94]. The disease is reported from 11 of 21 municipalities, mostly in the coastal area (Figures 2 and 3). The highest incidence is recorded in Ulcinj and Bar, and 54% of cases were 0–7 years old. According to the WHO-GHDR dataset, there were 36 VL cases between 2005 and 2020, including 20 autochthonous cases and no CL cases during the period 2013–2020 (Table 1) [32].

Between 2009 and 2019, notification of leishmaniasis was mandatory in domestic animals and disease was reported to be present [62].

Status of leishmaniases in Serbia
Human leishmaniases are not notifiable in Serbia.

Scientific literature reports one possible locally-acquired case from southern Serbia between 2001 and 2007 [95]. According to the WHO-GHDR dataset, there were five VL cases between 2009 and 2016, two of which were autochthonous. No CL cases were reported during the period 2013–2016 and no information is available outside of this period (Table 1) [32].

Leishmaniasis in domestic and wild animals is officially notifiable and no cases were reported to the WOAH [62]. Seroprevalence in ELISA studies in 220 dogs in the northern region of Vojvodina between 2009 and 2013 was 15% (Figure 5) [96]. *Leishmania* spp. DNA was detected by PCR in 7% of 216 spleen samples from golden jackals collected in Branicevski, Grad Beograd, Podunavski and Podunavlje districts in Central Serbia.

Leishmania infantum DNA was detected by PCR in three (4%) blood-fed *P. papatasi* females from Vojvodina collected between 2013 and 2015 [97].

Status of leishmaniases in Romania
Human leishmaniases are notifiable, but otherwise there is no specific national control programme in place [22]. Human VL was common in southern Romania until the 1960s when mass insecticide used for malaria control eliminated leishmaniases. According to the WHO-GHDR dataset, there were three autochthonous and two imported VL cases and two imported CL cases detected during the period 2013–2020 (Table 1) [32].

The first new autochthonous CanL was described in 2014 in the southern province of Valcea [98], and PCR testing of conjunctival swabs determined a prevalence of 8% in dogs from this locality [99] (Figure 5). Prior to 2014, three of 29 dogs from Bucharest exported to Germany were found to be IFAT seropositive [100]. More recently, 8% of dogs from the eastern county of Galati tested positive using an in-house ELISA [101], and 9% and 11% respectively of blood and conjunctival swab samples from dogs in the Arges district, west of Bucharest, tested PCR-positive [102]. *Leishmania* spp. DNA was detected by PCR in the bone marrow of one of 36 golden jackals from the south west county of Dolj [103].

Status of leishmaniases in Ukraine
Leishmaniases are notifiable in humans and dogs, but otherwise there is no specific national control programme in Ukraine. Sporadic VL cases have been reported in the last two decades in Ukrainian citizens from Kyiv, Lviv and Sumy, who most likely acquired the infection in the Crimean Peninsula, in the coastal area around Feodosiya, Sulak and Alushta (Figure 3) [74]. Alvar et al. [17] reported an average of two VL cases annually in Ukraine during the period 2005–2008, and underreporting was considered moderate [17]. According to the WHO-GHDR dataset, there were 14 VL and 26 CL cases between 2005 and 2020, including one autochthonous VL (Table 1) [32].

Visceral leishmaniasis was described in an eight-month-old boy in Ukraine who had presumably acquired the infection congenitally from his Ukrainian mother who was possibly infected in Spain [104].

Status of leishmaniases in Moldova
No information on leishmaniasis among humans could be retrieved for Moldova. Given the epidemiological situation in those countries neighbouring Moldova (Ukraine and Romania), the occurrence of sporadic cases of human leishmaniasis cannot be excluded.

Leishmaniasis in animals is a notifiable disease, however no autochthonous cases among have been reported in animals [22]. There is no surveillance or specific control measures applied for animal leishmaniasis.

Status of leishmaniases in countries with moderate-to-high endemicity

Status of leishmaniases in Albania
Notifications of both HumL and AniL are mandatory and there is surveillance of HumL. There is no national control programme but there are control activities involving indoor residual spraying. Leishmaniases are traditionally endemic diseases in Albania and their incidence and geographical spread rose noticeably during the period 1997 to 2001 [105]. Leishmaniasis is considered to be an emerging disease in Shkoder, Lezhe, Librazhd, Tirana and Berat [22,31].

Human leishmaniases

In 2004–2008, the average annual number of VL and CL cases reported was 114 and six cases, respectively, with VL considered to be mildly underreported [31]. In 2016 and 2018, Albania reported 15 and 45 VL cases, respectively, and six and two CL cases, none of which were imported [31,32]. According to the WHO-GHDR dataset, the median annual VL incidence decreased (from 3.77 for the period 2005–2008 to 0.52 between 2013 and 2016), before increasing slightly to 0.77 for the period 2017–2020. All cases reported between 2013 and 2020 were autochthonous. Incidence of CL has remained below or equal 0.1 since 2005 and all cases have been autochthonous (Table 1) [32].

According to the WHO-CP, the age distribution of VL cases in Albania in 2016 was as follow: 47% of the cases were below five years of age, 20% of the cases were five to 14 years and 33% were over 14 years. Similarly, the age distribution of CL cases in Albania in 2016 was as follows: 17% of the cases were below five years of age, 33% were between five and 14 years and 50% of the cases were over 14 years.

Visceral leishmaniasis has been reported from all districts, with high incidence in urbanised areas in Shkodër and Lezhë in the north, Tirana in the centre and Lushnjë, Fier, Berat and Vlorë in the south (Figure 3) [30].

Animal leishmaniases

IFAT seroprevalence and PCR prevalence in blood samples from police dogs that had travelled around the country were 12% and 3%, respectively [32]. ELISA seroprevalence was 10% in healthy dogs from the southern mountainous districts of Girokastra, Permeti, Tepelana and Erseka and coastal Saranda [106]. A similar seroprevalence of 9% was detected by IFAT in privately-owned dogs in Tirana, while parasite DNA was detected in 5% of the blood samples using quantitative PCR [107]. A CanL survey in nineteen areas with reported human cases revealed 3% ELISA seroprevalence and some dogs had clinical signs [108] (Figure 5).

During the period 2008–2010, IFAT and blood PCR prevalence in free-roaming cats from Tirana was 0.7% and 0%, respectively [109].

Sand fly infections

The infection rate in dissected *P. neglectus* females from Lezhe was 3% in 2011, and 4% by PCR in an earlier study [110]. In Permet in 2006, minimum infection rates in pooled samples were 2% in *P. neglectus* and 33% (n=3) in *P. tobbi* [110]. The minimum infection rate in pooled sand fly samples collected in Lezhe and Brine was 0.3% [111].

Status of leishmaniases in Bulgaria

Leishmaniases are mandatorily notifiable in Bulgaria and the surveillance system is comprehensive. There is a national control programme that includes the diagnosis of infection in humans, including travellers and migrants with clinical signs. It also includes a focus on diagnosis in stray dogs [22]. Leishmaniasis is historically endemic in the south of the country and from 1988 to 2008, 17 (16%) VL patients died due to late diagnosis and treatment, and a lack of awareness of the disease [17].

Human leishmaniases

Between 1988 and 2008, 110 VL cases were reported with peaks of 10-14 cases in 2001, 2002 and 2005 and most cases came from the Thracian Lowlands, Stara Zagora and the Valley of the Struma River (Figure 1 and 3) [17,112,113].

Alvar et al. [17] reported an annual mean number of 7 VL cases in 2004–2008 with underreporting considered mild, and the estimated incidence was 0.09. According to the WHO-GHDR dataset, the median annual incidence of VL reported between 2005 and 2020 fluctuated between 0.01 (2017–2020) and 0.13 (2013–2016) and it was 0.028 and 0.014 for CL in 2013–2016 and 2017–2020, respectively, with most cases being imported (Table 1) [32].

The percentage of VL cases by age group were 23% in those <5 years old, 3% for those aged 5–15 years and 74% for those >15 years old. Cases came from 12 of 28 NUTS3 sub-divisions and the cumulative incidence per 100 000 population was highest - 9.5 (30 cases) - in Blagoevgrad (Petrich Municipality) and Sofia - 0.2 (4) (Figure 3) [114].

Animal leishmaniases and sand fly infections

Canine leishmaniases are sporadically reported in Bulgaria, with two clinical cases in 2006 in Petrich, and 10 other cases in 2006 and 2007 in Blagoevgrad and Haskovo (Figure 5) [115]. In two countrywide epidemiological studies carried out using RICT, ELISA and IFAT, no dogs were found to be conclusively seropositive [116,117]. According to the WOAH website, presence of disease in both domestic and wild animals during the period 2009–2018 was unknown, although it is stated that leishmaniosis in domestic animals was a notifiable disease between 2014 and 2019 [62].

No sand fly infection studies are available.

Status of leishmaniases in North Macedonia

Leishmaniases are endemic in the country, and an annual average of seven human VL cases was reported between 2005 and 2009, with under-reporting considered to be mild [17]. According to the WHO-GHDR dataset, the median annual VL incidence was between 0.34 and 0.39 in the period 2005–2016 and 0.51 between 2017 and 2020. There were no CL cases during the period 2013–2020 (Table 1) [32].

An epidemiological study in 410 dogs in the capital Skopje revealed a 27% estimated and 20% true (adjusted for test validity) ELISA seroprevalence, and 5% of the dogs had clinical signs of CanL [118].

Status of leishmaniases in Croatia

Leishmaniases are notifiable in humans and animals and there is a comprehensive surveillance system. The national control programme includes a regular serological testing of dogs [17,22,62]. Leishmaniases are endemic in the coastal area of central and southern Dalmatia and on the islands of the Adriatic. After a drastic reduction in the incidence of HumL and CanL following insecticidal anti-malarial campaigns in the 1950s, the disease re-emerged in the 1990s, with 35 cases (23 VL and 12 CL) registered between 1994 and 2006, and a substantial number occurring during the 1992-96 war and post-war period [17].

Human leishmaniases

Alvar et al. [17] reported an annual average of five VL cases and two CL cases between 2004 and 2008, with underreporting considered to be mild. The corresponding incidences were 0.12 for VL and 0.05 for CL (Table 1). According to the WHO-GHDR dataset, between 2005 and 2020 there were 24 VL cases, 21 of which were during the period 2005–2008. Between 2005 and 2020, there were 27 CL cases, most of them occurring during the periods 2005–2008 and 2013–2016 (Table 1) [32].

A serological survey in healthy people carried out in 2007-2009 revealed that 11% tested positive using ELISA. Almost all positives were from the Adriatic coast, particularly Central Dalmatia (22% seroprevalence) and some from as far north as Istria and Primorje (4% seroprevalence) where no autochthonous VL cases had been reported at that time (Figure 3) [119].

Animal leishmaniases

Between 2009 and 2019, WOAH notification of leishmaniasis in domestic and wild animals was mandatory, and although the disease was reported in domestic animals in Croatia between 2009 and 2016, there were no reports in either animal groups during the period 2017–2019. The number of animal cases notified ranged between 71 (2009) and 20 (2016) [62].

Canine leishmaniases has been reported in the central and southern Dalmatian NUTS3 sub-divisions of Splitsko-Dalmatinska and Dubrovacko-Neretvanska (Figure 5) [105].

In a survey in central Dalmatia seroprevalence in random dog populations was 15%, with most positives coming from the CanL focus town of Rudine where seroprevalence reached 31% [120,121]. In a later nationwide study seroprevalence was 1% and all seropositive dogs were from the Dubrovnik area in southern Dalmatia [122].

In a study carried out during the period 2011–2013, a PCR-positive black rat was detected in Istarska on the northern Adriatic coast [123].

Status of leishmaniases in Cyprus

Leishmaniases are mandatorily notifiable in humans and dogs and leishmaniasis is considered to be an emerging disease. Comprehensive surveillance is carried out, but there is no national control programme [22].

By the end of the twentieth century, leishmaniases were almost eliminated following malaria and *Echinococcus* control campaigns. Visceral leishmaniasis by *L. infantum* re-emerged in 1996 in dogs and foreign tourists having visited the southern part of Cyprus, but not in the local population. In addition, human CL cases were detected in the northern part of Cyprus.

Human leishmaniases

Alvar et al. [17] reported an annual average of two VL cases and one CL case between 2004 and 2008, with underreporting considered to be mild. The corresponding incidences were 0.26 and 0.13 per 100 000 people, respectively. According to the WHO-GHDR dataset, there were four and five autochthonous VL and CL cases respectively reported between 2013 and 2020. There were no VL or CL imported cases reported during the period (Table 1) [32].

One concern was the identification in 2006 of six human cases of *L. donovani* infection, four CL and two VL cases, [124] and later, a family cluster of CL cases in the southern prefecture of Pafos (Figures 3, 4 and 7) [125]. This is the only place where this species has been described in Europe, and the origin of the infection is unknown [17,125]. However, none of the 635 humans from the southern part of Cyprus analysed for *Leishmania* spp. antibodies using ELISA and IFAT in 2005–2006 were seropositive [124]. In the northern part of Cyprus, 1% of 249 humans analysed using direct agglutination tests and rk39 antibody tests were seropositive [126].

Animal leishmaniases

Canine leishmaniases occurs across Cyprus, with a high incidence in Pafos (Figure 5). Between 2009 and 2019, notification of leishmaniasis was mandatory in domestic animals. The disease was also notifiable in wild animals between 2013 and 2019, however no cases were reported [62].

Two antibody studies carried out in the southern part of Cyprus showed comparable results [105,124]. The first study, involving 900 dogs, showed a seroprevalence of 12% by IFAT and 15% by ELISA. The second study, involving 2 956 dogs, showed a seroprevalence of 20% by ELISA. Leishmaniasis prevalence in blood samples from cats in the southern part of Cyprus was 4% using ELISA and 2% using PCR [127]. In the northern part of Cyprus IFAT seroprevalence in dogs was 2% [128].

Antibodies against *Leishmania* spp. were detected in 7% of 622 rats tested during the period 2000–2003 [129].

Sand fly infections

Leishmania infantum DNA was reported from *P. tobbi* in the northern part of Cyprus [130].

Status of leishmaniases in Malta

Leishmaniases have been mandatorily notifiable since 1946 [62] and surveillance and control involve testing dogs from shelters and households, and strays using serological and PCR methods [22]. Malta is a traditionally VL endemic country, particularly the island of Gozo. Incidence was greatly reduced in the 1960s following a specific leishmaniases control programme. Cases of CL were first detected in the 1980s and subsequently became more prevalent (unpublished data).

Human leishmaniases

Between 2004 and 2008, the average annual number of VL and CL cases were two and zero, respectively, with underreporting considered to be mild [17]. The corresponding VL incidence was 0.49 per 100 000 inhabitants. According to the WHO-GHDR dataset, between 2005 and 2020, 18 VL cases were reported, nine of which occurred during the period 2017–2020 (eight autochthonous and one imported). Similarly, 54 CL cases were reported between 2005 and 2020, including 36 cases during the period 2005–2008 (Table 1) [32]. During this same period, Pace et al. [131] reported 11 paediatric cases (eight VL and three CL cases) (Figures 3 and 4).

From 2009 to 2018, 18 VL cases (0–4 annually), aged 13 to 81 years, were reported in Malta's hospitals [132].

Animal leishmaniases and sand fly infections

Presence of the disease in domestic and wild animals was reported between 2009 and 2019 and between 2010 and 2019, respectively [62]. During the period 2013–2014, CanL seroprevalence assessed by RICT was 16% in 887 dogs from a veterinary clinic and some dogs had typical clinical signs (Figure 5) [133].

No sand fly infection studies were reported.

Status of leishmaniases in Greece

Leishmaniases are notifiable in both humans and animals. Control programmes are implemented by local authorities, and focus on stray dog population control and application of insecticides and treatments or euthanasia on welfare grounds for dogs that cannot be treated. Insecticide campaigns against malaria vectors in the 1940s reduced leishmaniases incidence drastically but it re-emerged after they were discontinued [4]. *Leishmania infantum* is now endemic in most parts of the country and causes VL and CL in humans and animals. Meanwhile, *L. tropica* was responsible for sporadic human CL [23] and CanL [4,43] in the early 2000s in Crete.

Human leishmaniases

Between 1998 and 2011, 664 leishmaniases cases were reported from 52 of the 57 prefectures (Table 2) and the mean annual incidence was 0.36 cases per 100 000 population, 93% were VL cases, and among these VL cases, 14% were aged 0–4 years and 10% were aged 5–14 years [134]. According to Alvar et al. [17], during the period 2004–2008, the average annual number of VL cases was 42, and for CL it was three, with underreporting of VL and CL considered mild. The corresponding incidences in 2004–2008 were 0.38 and 0.03 per 100 000 inhabitants, respectively. In 2018, there were 53 VL cases and one CL case and the corresponding incidence was 0.49 and 0.01 per 100 000 inhabitants, respectively (unpublished data). According to the WHO-GHDR dataset, during the period 2009–2012 the median annual VL incidence rose sharply from 0.31 per 100 000 inhabitants to 0.67 in 2013–2016 before decreasing to 0.43 for the period 2017–2020; most cases were autochthonous (Table 1). The CL incidence ranged between 0.023 and 0.027 per 100 000 inhabitants between 2005 and 2016, and was 0.004 for the period 2017–2020 (Table 1) [32].

According to Alvar et al., during the period 2009–2018, 633 HumL cases were reported to the Hellenic National Public Health Organization, including 38 (6%) imported cases (25 CL and 13 VL cases), and 50 (8%) cases of VL with undetermined importation status. The mean annual number of notified cases was 61 (Table 3) [135]. The majority were VL cases (94%) and were autochthonous (93%). Annual median incidence was 0.56 cases per 100 000 inhabitants (Table 3), and it was 0.40 in 2009–2012 and 0.71 in 2013–2018 (p=0.011). The male/female ratio was 63/37 for VL and 60/40 for CL. The age distribution of VL cases was 14% (0–4 years), 9% (5–14 years), 52% (15–65 years) and 25% (>65 years). The age distribution of CL cases was 12%, 27%, 51% and 9%, respectively. A total of 136 of 532 patients (26%) were immunosuppressed, with the cause provided for 83 patients and the most frequent causes were cancer and rheumatoid arthritis. The HIV infection status of the patients was not reported.

Cases during the period 2009–2018 were from 48 of the 52 NUTS3 sub-divisions (Table 2) (Figures 4-7). The mean annual incidence was highest in Larisa (2.8 per 100 000 inhabitants), in the eastern central region of Greece's mainland, followed by Fokida (1.9) further south, Dytiki Attiki (1.6) in the west of the Attika region, and Karditsa-Trikala (1.6) west of Larisa (Table 2).

In 2003–2004, seroprevalence in healthy adult people in the northern Greek regions of Macedonia and Thrace, assessed with IFAT and ELISA, was 3% (43/1 525) [136].

Animal leishmaniases

According to the WOAH, between 2009 and 2018, notification of leishmaniasis was mandatory in both domestic and wild animals. The disease was present in domestic animals, although in 2013 it was said to be limited to one or more zones of the country [62]. No cases were reported among wild animals.

Numerous studies have reported clinical cases in dogs caused by *L. infantum* from northern, central and southern areas of Greece between 2009 and 2020 [105,137-141]. Some studies compared the validity of diagnostic tests [141-143] and others assessed treatment efficacy [139,144]. A dog with VL from Crete was found to be infected with *L. tropica* and required two miltefosine treatments [145].

Similarly, many epidemiological studies in random dog populations have been carried out across Greece (Table 4). In a nationwide survey involving 5 772 dogs between 2005 and 2010, seroprevalence using IFAT was 22%, ranging between 1% and 50% in different NUTS3; 25% in males, 18% in females, 27% in strays and 19% in dogs attending veterinary clinics. Of 165 *Leishmania spp.* strains, 164 were *L. infantum* and one was *L. tropica* [4]. In another countrywide study, IFA and ELISA seroprevalence was 20% [146]. In dogs from Karditsa, PCR prevalence in blood samples was 62% and IFAT seroprevalence 14% [141]. In contrast, Hofmann et al. [147] estimated a 25% RICT seroprevalence and 0% PCR prevalence in blood samples from shelter dogs on Crete. However, the prevalence of CanL on Crete is among the highest in Europe and is increasing [148]. In a recent study, RICT and ELISA seroprevalence on Crete ranged between 30% and 20%, respectively [142].

Leishmania prevalence in cats has been investigated in stray and household animals from several places in Greece with different diagnostic techniques (Table 4); IFAT seroprevalence ranged between 0% and 15% and PCR prevalence was 0–20% in blood samples and up to 41% in skin and lymphoid tissue [149-152].

Leishmania infections have been investigated in other wild and domestic species and estimated prevalences according to the host species were (Table 4): (i) foxes: 60% by PCR (lymphoid tissue and blood) and 33% by IFAT (serum) [153], (ii) lagomorphs: 0–30% by PCR (lymphoid tissue), 0–29% by IFAT/ELISA and 0% by microscopy of spleen smears [154-156], (iii) mink: 2% by PCR (lymphoid tissue), 20% by ELISA and 0% by microscopy of spleen smears [156], (iv) mice and rats: 0–23% by PCR (lymphoid tissue), 0–70% by ELISA and 0% by microscopy of spleen smears [157,158], (v) equines: 0–0.4% by ELISA [41,159] and (vi) sheep, goats and cattle: 0% IFAT/ELISA [160,161].

Sand fly infections

Leishmania spp. infection in individual *P. tobbi*, *P. perfiliewi* and *P. simici* specimens was analysed by PCR at two refugee camps in Thessaloniki and *L. donovani* complex species and *L. tropica* were detected in 7–47% and 13–20% of the sand fly specimens, respectively [52] (Table 27). Prevalence of *Leishmania* spp. infection in sand flies in other studies involving mainland Greece and the Greek islands ranged from 0 to 0.5% [23,145,162,163], and the minimum *L. infantum* infection rates in a pooled *P. perniciosus* and *P. neglectus* sample in Crete was 0.3% [164] (Table 5).

Status of leishmaniases in Italy

Leishmaniases in humans and animals are notifiable. Italy has national guidelines and a national control programme incorporating integrated surveillance of human and animal cases, and control measures such as treatment of stray and shelter dogs and usage of insecticides [22,53] (unpublished data). It is the country with the highest CanL seroprevalence in Europe. In the 1990s, human leishmaniases incidence rose from around 50 cases per 100 000 inhabitants annually to 215 in 2000 and 204 in 2004. This was associated with the HIV epidemic, an HIV-unrelated outbreak in the Campania region and a general increase in VL in the country [165].

In addition to the traditional endemic areas, including rural and hilly peri-urban areas along the north-west coast (Liguria), central and southern Italy (Tirrenian, southern Adriatic and Ionian Sea), Sicily and Sardinia, incidence has also been on the rise in Emilia-Romagna and new CanL and autochthonous HumL foci have been detected in previously non-endemic northern continental regions of Piedmont, Valle d'Aosta, Lombardy, Veneto, Trentino Alto-Adige and Friuli-Venezia Giulia [22,165]. Similarly, sand fly vectors and CanL have spread into previously non-endemic areas in the north of the country [166].

Human leishmaniases

In 2004–2008, the average annual number of VL cases was 134, and similarly, for CL it was 49 cases, with underreporting of VL and CL considered mild [17]. Based on the WHO-CP, in 2018 Italy notified 145 cases, including 74 new VL cases and 71 CL cases. Of these, 3% of the VL cases and 1% of the CL cases were imported. The corresponding VL and CL incidence were 0.23 and 0.08 per 100 000 inhabitants in 2004–2008 and 0.12 and 0.12 in 2018. According to the WHO-GHDR dataset, between 2005 and 2016 the median annual incidence of VL ranged between 0.10 and 0.19 per 100 000 inhabitants and during the period 2017–2020 it was 0.86 (Table 1). Similarly, between 2005 and 2020 CL incidence per 100 000 inhabitants ranged between 0.04 and 0.13 (Table 1) [32].

For the period 2016–2018, 23% of those affected were females (43%) for VL, and 40% (32%) for CL [53] (unpublished data). In 2016 and in 2018, the age distribution of VL cases in Italy was as follows: 8% and 16% of the cases were below five years, 6% and 6% of the cases were five to 14 years of age and, 67% and 78% of the cases were over 14 years [53] (unpublished data). Similarly, the age distribution of CL cases in Italy in 2016 and in 2018 was as follows: 0% and 14% of the cases were below five years, 2% and 7% of the cases were five to 14 years and 98% and 79% of the cases were over 14 years of age.

Hospital discharge records for leishmaniases between 2011 and 2016 included 2 509 cases, 81% of which were VL from 19 of the 20 regions (NUTS2 subdivisions), with no cases from the Aosta Valley and the highest incidence in Sicily (1.9 cases per 100 000 inhabitants) and Liguria (1.6) (Table 6). Females accounted for 29% of cases and 10% were children <5 years old and a further 5% were aged 5–14 years (Table 7) [167].

Clinical cases reported in the scientific literature between 2009 and 2020 were from 24 of 110 provinces (NUTS3) in 11 regions. Most cases involved *L. infantum* but other species were from the *L. donovani* complex and *L. guyanensis* complex (Table 8) (e.g. [167-173]).

Prevalence in epidemiological studies of healthy blood donors differed between diagnostic techniques and places ranging from 0–36% by IFAT, 7–39% by western blot seroprevalence and 4–11% by PCR in blood samples (Table 9).

Animal leishmaniases

According to WOAH, the disease was reported to be present in domestic and wild animals during the periods 2009–2014 and 2011–2017, respectively [62].

Nationwide estimates of the number of infected dogs were provided for 2009–2019 [174] and infected cats for 2017–18 [175] (Table 10). Infected dogs came from 110 out of the 111 NUTS3 sub-divisions and cats from 32 NUTS3 sub-divisions. The ratio of males to females was 57/43 for dogs and 62/38 for cats. The mean age range was 4.6 (0–12) years for dogs and 3.6 (0.6–12) years for cats. Canine leishmaniases seroprevalence decreased with time and was highest in 2011 and 2012, depending on the region [174].

Seventy-four prevalence studies in random populations of dogs, cats and other domestic and wild animals (lagomorphs, carnivores and rodents) were performed in 46 NUTS3 sub-divisions (Tables 15a, b and c). In dogs, seroprevalence ranged from 0% to 58% (<20% in most studies) and was highest in Sicily and the north-west of the country. PCR prevalence in blood samples was similar or below seroprevalence, and in two studies it was 25% in lymphoid tissue (Table 11a) [176-184]. In cats, seroprevalence ranged from 0–33% and PCR prevalence was 0–8% in blood samples and 0–4% in lymphoid tissue (Table 11b) [185-188]. In contrast, in wildlife PCR prevalence in lymphoid tissue ranged from 0% in Sicily to 52% in foxes in Pisa (Table 11c) [189,190].

Sand fly infections

Leishmania infantum was identified in *P. perniciosus*, *P. papatasi*, *P. neglectus* and *P. perfiliewi* (Table 12) [191-194].

Status of leishmaniases in France

Leishmaniases are not notifiable; nonetheless there is a comprehensive surveillance scheme for HumL organised by the National Reference Centre for leishmaniases which was created in 1999. There is no official control programme in place for leishmaniases. Traditional endemic areas are the south and south-east regions of Pyrénées Orientales, Cévennes, Provence, Alpes-Maritimes and Corsica, and cases come from rural areas and from the metropolitan areas around Nice and Marseille. Leishmaniasis is considered an emerging disease, particularly in the south-west regions [22]. During the period 2009–2020, cases of autochthonous and non-autochthonous human and animal leishmaniasis were reported from 25 of the 96 departments (NUTS3) in mainland France (Table 17; Figures 5 and 6).

Human leishmaniases

Between 1999 and 2012, 1 471 cases were reported, including 85% VL, 12% CL and 3% mucosal leishmaniasis, and 78% of the cases were imported. The 317 autochthonous infections were acquired in 14 NUTS3 areas in the south of France [195]. Among these autochthonous infections, the male-to-female ratio was 1.8, and 23% of the cases were <5 years old. The mean annual number of autochthonous cases was 23. The annual incidence per 100 000 population in affected regions was 0.23 (ranging from 0.02 in Aude to 0.85 in South Corsica) (Table 13) [195]. Alvar et al. [17] reported an annual average of 18 VL cases and 2 CL cases between 2004 and 2008, with under-reporting considered to be mild. The corresponding country incidences for VL and CL were 0.03 per 100 000 inhabitants and <0.01, respectively. Based on the WHO-GHDR dataset, the median annual VL incidence per 100 000 inhabitants ranged between 0.19 and 0.29 during the period 2005 to 2013, before increasing to 0.45 in 2017–2020 with a large number of imported cases (Table 1). As for CL incidence, this rose sharply from <0.01 in 2005–2012 to 0.14 in 2013–2016 and 0.27 in 2017–20, with the majority of cases being imported (Table 1) [32].

Between 2009 and 2019, 176 autochthonous cases were reported (67% VL, 24% CL and 9% mucosal leishmaniasis) (Table 14). The median (range) annual number of autochthonous cases was 15 (11–31). The median annual incidence was 0.02 (0.02–0.05), in 2009–2012 it was 0.03 and in 2013–2019 it was 0.02 (p=0.088) (Table 14).

Leishmania seroprevalence analysed by western blot in serum samples collected between 2001 and 2010 from a random selection of Marseille hospital patients was 28% (132/472) [196].

Animal leishmaniases

In a review of serological surveys in non-imported dogs between 1965 and 2007, three foci were identified for CanL (i) foothills of the Cévennes Mountains and other southern ranges of the Massif Central facing the Mediterranean, (ii) south-west foothills of the Maritime Alps and (iii) the hilly area of the Côte d'Azur near the Italian border. The most affected departments were Ardèche, Gard, Hérault, Bouches-du-Rhône, Var and Alpes-Maritimes. In total, autochthonous cases in France have been reported from 21 NUTS3 sub-divisions, including some as far north as Indre-et-Loire (Table 13) [197].

A total of 140 military dogs wearing deltamethrine-impregnated collars from Var, Bouches-du-Rhône and Corsica were tested for canine leishmaniases. The result was 1% ELISA positives, 14% western blot positives and 41% PCR positives were reported, with 50% positives overall [198]. A 20-year serological study in military dogs reported an annual serological and clinical CanL incidence of 43% and 21%, respectively, before insecticide collars were used and 6% and 3%, respectively, after insecticide collars were introduced [199].

During the period 2006-2012, *Leishmania* prevalence in 92 foxes from Var, analysed by PCR in lymphoid tissue samples was 9%, and none of the animals had lesions compatible with leishmaniases [200].

In a survey among French and Spanish veterinarians [201], the latter confirmed an average of 27 CanL cases per year, compared with seven in the south of France and 0.4 in the north of France. However, veterinarians in northern France have reported a large increase in the number of CanL cases over the past 10 years [201]. In addition, 76% of veterinarians indicated that they had never received information regarding CanL and HumL cases occurring in their region or country, and 88% admitted never reporting a CanL case. The authors recommended the creation of an easy-to-use online network where both veterinarians and physicians could report leishmaniasis cases. A similar system operates in the USA [201].

Sand fly infections

In Marseille (Bouches-du-Rhône) in 2009–10, the minimum infection rate in pooled sand flies (88% *P. perniciosus*) was 0.6% [202].

Status of leishmaniases in Spain

Leishmaniases are notifiable diseases in humans and animals (sub-national level only) and there is a comprehensive surveillance scheme and a control programme based on treating infected cases and administering insecticides to dogs.

The HIV epidemic had a major impact in the resurgence of human leishmaniases in Spain, with almost 2 000 cases between 1990 and 2000 [17]. Canine leishmaniases is considered an emergent disease in Spain with increased incidence in some endemic areas and new cases in previously non-endemic northern areas [203] and at higher altitudinal ranges in southern Spain [204]. Infections in humans and animals have been reported in every province (NUTS3) sub-division (Figures 5 and 6).

Human leishmaniases

Between 2004 and 2008, the average annual number of VL cases notified was 117, with underreporting considered mild, and no CL cases reported [17]. In 2014, Spain notified 206 cases (106 VL and 100 CL) and in 2017 Spain 387 cases (199 VL and 188 CL); in 2017, 2% of the VL cases and 11% of the CL cases were imported. The estimated incidences per 100 000 inhabitants in 2004–2008, 2014 and 2017 were 0.26, 0.23 and 0.46 for VL and 0.00, 0.22 and 0.40 for CL, respectively. According to the WHO-GHDR dataset, the median annual VL incidence between 2005 and 2020 was relatively stable, ranging between 0.38 and 0.51 (Table 1) [32]. The CL incidence was between 0.02 and 0.03 for the period 2005–2012 and increased to 0.22 in 2013–2016, subsequently reaching 0.40 in 2017–2020 (Table 1). Most of these CL and VL cases were autochthonous [32].

For the years 2014–2017 the percentage of affected females was 28–34% for VL and 37–45% for CL. Age-specific percentages of leishmaniases for these years were, 16–26% for <5 years, 2–3% for 5-14 years and 82–68% for >14 years for VL. Similarly, for CL it was 6–11% for <5 years old, 4–15% for 5–14 years and 70–90% for >14 years [32] (unpublished data).

Hospital discharge records for leishmaniases between 2000 and 2018 included 10 287 records from 5 848 people (average of 308 per year) and the proportions of clinical forms were 79% VL, 2% CL and 2% mucocutaneous leishmaniases and in the remaining 17% the clinical form was not recorded (Table 15) [205]. Sixteen percent of the cases were four years or younger, 2% were between 5 and 14 years and 82% were 15 years or older; 73% of the patients were male (Table 16). The median (range) annual incidence was 0.69 per 100 000 inhabitants (0.51-0.87) (Table 17); 0.76 in 2000–2008, 0.61 in 2009–2012 and 0.65 in 2013–2018. Cases came from every province and incidence was highest in the eastern and southern Mediterranean coastal provinces, the Balearic Islands and the inland provinces of Jaen, Córdoba, Toledo and Madrid (Table 15). The distribution of cases according to demographic variables was similar to those provided in the WHO-CPs (Table 16).

The following Leishmania species were reported among autochthonous and imported cases: *L. infantum*, *L. tropica*, *L. major*, *L. braziliensis* and *L. panamensis* (Table 18).

Nine studies investigated the prevalence of *Leishmania* infection in blood donors, HIV-positive patients, those with organ transplants and people attending primary health care centres for reasons other than leishmaniases, and prevalence ranged between 0–20%, depending on the population and diagnostic technique used (Table 19).

Animal leishmaniases

According to WOAH, there were reports of AniL in domestic animals between 2009 and 2019 [62] and between 2010 and 2013 the disease was also detected in wild animals.

Twenty-nine articles reported clinical cases of leishmaniases by *L. infantum* in dogs [206-210], cats [210,211], hares [212], ferrets [213], wallabies [214] and orangutans [215], and one article also described subclinical infections in beech martens, brown bear, brown rat, domestic cat, rabbit, genet, red fox, wood mouse and Iberian wolf [216]. Canine leishmaniases was reported from 11 provinces, the median (range) of the mean age reported for dogs was seven (4–11) years old, and similarly, for cats it was seven (2–21) years.

Forty-three articles provided *Leishmania* infection prevalence data in randomly selected populations of 24 animal species including dogs, cats and wildlife (fox, wolf, mustelids, lagomorphs and rodents). Prevalence was mostly investigated with serological assays (IFAT, ELISA, RICT and western blot) and PCR in blood, skin, hair and lymphoid-rich tissue (lymph node, bone marrow, spleen and liver). Tables 24a, b and c, show the mean (range) prevalence of leishmaniases in dogs, cats and wildlife, according to the main diagnostic techniques. The mean seroprevalence for dogs varied between and within provinces, ranging mostly from 0% to 30%, and the highest prevalence was with PCR tests in skin and lymphoid tissue samples (Table 20a). In cats, seroprevalence and PCR prevalence in blood samples ranged between 1–16% and was 26% by PCR in lymphoid tissue in the Balearic Islands (Table 20b). Most wildlife studies used PCR tests, particularly in lymphoid tissue samples, from asymptomatic animals. Median PCR prevalence ranged between 0% and 52% in lymphoid tissue, 0–33% in skin and 26–60% in hair samples (Table 20c).

Sand fly infections

Between 2002 and 2018, *L. infantum* was identified in the vectors *P. ariasi* and *P. perniciosus* with infection rates ranging from 6% to 79% when analysed by PCR and 3% and 7% in dissected specimens (Table 21). It was also identified in *P. langeroni*, *P. sergenti* and *S. minuta*. *Leishmania tarentolae* from reptiles was detected in 1–3% of *S. minuta.* The highest *P. perniciosus* infection rates were found in the HumL community outbreak in Madrid [217].

Status of leishmaniases in Portugal

Visceral leishmaniasis has been mandatorily notifiable in humans since the 1950s and CanL only for cases suspected by municipal veterinarians when examining dogs during rabies control campaigns. Human CL is uncommon and is not notifiable. In 2008, the Portuguese National Leishmaniases Observatory was created to implement a CanL surveillance network and leishmaniases control, based on a 'One-Health' approach [37]. According to the WHO-CP on leishmaniasis in Portugal [17], there is a leishmaniasis reservoir control programme with obligatory diagnosis and treatment, or euthanasia of all suspected dogs.

By 1970, anti-malarial campaigns had reduced incidence to very low levels, but leishmaniasis re-emerged in the 1990s with a high incidence of HIV-*Leishmania* co-infections. Leishmaniases are present throughout the country with three traditional foci: Alto Douro region in the north, the Algarve in the south and suburban areas of Lisbon (where feline prevalence reached 30%) [37].

Human or animal cases have been reported in 20 of the 25 NUTS3 sub-divisions, with no cases in Alto Tamega and Ave in the north, Alentejo Litoral in the south, Madeira and the Azores (Figures 5 and 6).

Human leishmaniases

Between 2003 and 2007, the average annual number of VL cases was 15, with underreporting considered mild [17]. According to the WHO-GHDR dataset, the median annual VL incidence per 100 000 inhabitants declined from 0.13 in the period 2005–2008 to 0.04 in 2013–2016, increasing to 0.06 in the period 2017–2020. There were 22 CL cases, the majority being autochthonous (Table 1) [32].

Hospital records for the whole of Portugal between 2010 and 2017 included 689 hospitalisations of 346 patients (36–59 patients per year); 73% of the patients were men (Table 22) [218]. Median annual incidence per 100 000 population was 0.41 (Table 22); 0.50 in 2010–2012 and 0.37 in 2013–2018. During this period, one hospital in Lisbon treated 24 HIV-*Leishmania* co-infected patients with amphotericin B with a 62% success rate and survival after five years was 46% [219].

None of the 229 asymptomatic volunteers from *Leishmania*-endemic Beira Baixa were positive by PCR and direct agglutination test in blood and serum samples [220]. Depending on the cut-off, seroprevalence analysed by IFAT ranged between 0–44% in owners of dogs without leishmaniases and 4–74% in owners of dogs with leishmaniases, but all samples were western blot-negative, suggesting IFAT lacked specificity in asymptomatic populations and that, according to results obtained, having a sick dog was not a risk factor [221].

Animal leishmaniases

According to WOAH, the disease was reported in domestic animals between 2009 and 2019 [62].

Seventeen articles and theses reported clinical cases and/or the performance of diagnostic tests, treatment and vaccination for mostly canine and feline leishmaniases [222-231].

Fifty-one articles and theses reported infections in random populations of dogs, cats, donkeys, horses and wildlife species including red foxes, Iberian wolves, European genets, Egyptian mongooses, mice and rats. The tests used included microscopy, PCR tests in blood and tissue samples and serological assays including IFAT, ELISA, RICT and direct agglutination tests [223,224,228,232-239]. Tables 27a, 27b and 27c present the medians and ranges of

leishmaniasis prevalence in dogs, cats and wildlife according to NUTS3 and regions of Portugal and the diagnostic technique used. In dogs, seroprevalence ranged between 0% and 56%, and was <20% in most studies; PCR prevalence in blood ranged between 0% and 69% and PCR prevalence in tissue ranged between 0% and 33% (Table 23a). In cats, seroprevalence ranged between 0% and 17%, with PCR in blood samples ranging between 0% and 25% and PCR in skin and buffy coat samples 0% and 5%, respectively (Table 23b). In wildlife, seroprevalence ranged between 0% and 6% and PCR prevalence in tissue samples between 0% and 33% (Table 23c).

Sand fly infections

Infection rates by PCR in individual sand flies were 4% in *P. ariasi* females from Médio Tejo, 0.1–0.2% in *P. perniciosus* and 0.1% in *S. minuta* from Algarve, 1.7% in *P. perniciosus* and 4.9% in *S. minuta* from Alentejo Central and Beja, and 0% in other sand fly species from these territories and two studies in the metropolitan area of Lisbon (Table 24) [240-246].

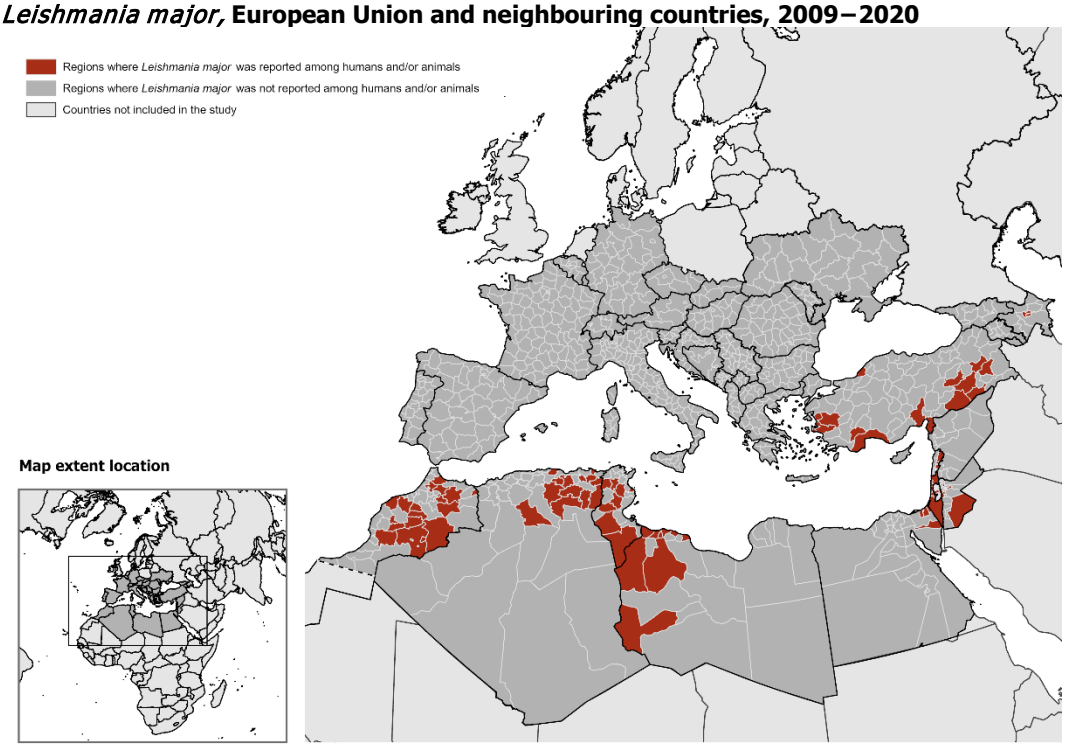
Figure 7. Geographical distribution of reported human and/or animal cases of leishmaniasis due to *Leishmania donovani s.s.*, European Union and neighbouring countries, 2009–2020

3.2.2 Status of leishmaniases in North Africa

General epidemiological features

Three *Leishmania* species, *L. infantum*, *L. major* and *L. tropica* are endemic in the region (Figures 2, 6, 8 and 9). They cause tens of thousands of HumL cases every year, mostly CL cases, and *L. major* is responsible for the majority of them.

Figure 8. Geographical distribution of reported human and/or animal cases of leishmaniasis due to *Leishmania major*, European Union and neighbouring countries, 2009–2020



Administrative boundaries: © EuroGeographics © UN–FAO © WHO
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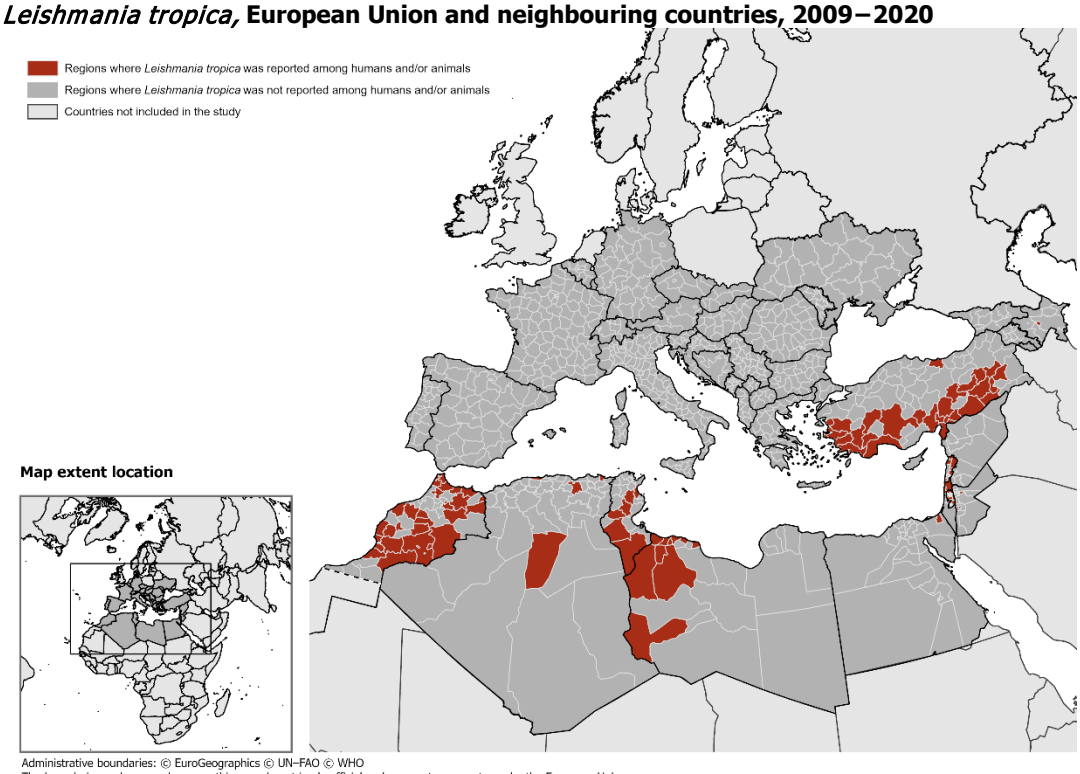
Figure 9. Geographical distribution of reported human and/or animal cases of leishmaniasis due to *Leishmania tropica*, European Union and neighbouring countries, 2009–2020



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Leishmania major is genetically homogeneous across the region [247]. It is transmitted by *Phlebotomus* (*Phlebotomus*) *papatasi* and rodent reservoir species in the region that include the fat sand-rat *Psammomys obesus* and the gerbil *Meriones* spp., which are species native to the semi-arid and arid climates of the northern Saharan fringe. They live in burrows that provide an ideal environment for sand flies to complete their life cycle and they reproduce rapidly in peri-domestic environments of rural communities.

In contrast, *L. tropica* transmitted by *P.* (*Paraphlebotomus*) *sergenti*, is a highly heterogeneous species and variants that present in northern Africa are different to those in the Middle East and Central Asia, namely the 'Aleppo-Syria' or 'Kabul-Afghanistan' *L. tropica* strains that typically establish anthroponotic and highly endemic urban cycles. Moreover, *L. tropica* in northern Africa also displays extensive variability, particularly in Morocco where this species is most prevalent, and at least eight isoenzyme profiles or 'zymodemes' have been described there. *Leishmania tropica,* which occurs in Algeria, Tunisia and Libya, is less diverse and, although it was given a separate species-status and named *L. killicki* in 1986, it is now considered part of a single *L. tropica* complex [247]. In addition to an anthroponotic life, in northern Africa *L. tropica* also establishes zoonotic cycles and putative reservoirs are gundi rodent species - *Ctenodactylus gundi* in Tunisia [248,249] and *Massoutiera mzabi* in Algeria [250].

Leishmania infantum is adapted to the humid and semi-humid zones of the northern fringe of these countries where it is transmitted by the *Larroussius* sub-genus species. Confirmed and suspected vector species include *Phlebotomus (Paraphlebotomus) alexandri, P. ariasi, P. langeroni, P. longicuspis, P. major s.l., P.* (*Transphlebotomus*) *mascittii, P. perfiliewi* and *P. perniciosus*. Vector species distribution varies among the countries; *P. perniciosus*, *P. ariasi* and *P. longicuspis* are the predominant vectors in Morocco, Algeria and Tunisia but are not found in Libya and Egypt. *P. major s.l.* has only been detected in Egypt and *P. mascittii* only in Algeria.

Since underreporting is inherent to CL, the dramatic rise in the number of leishmaniases cases reported in northern Africa in the 1980s and 1990s may be partly due to improved CL reporting. Nevertheless, there is ample evidence that leishmaniases have expanded geographically as a result of human activities, particularly movement of people due to development projects involving massive mobilisation of water resources into arid areas, infrastructure building and urbanisation. Risk factors typically associated with outbreaks include poverty, precarious housing, close human-animal cohabitation in rural areas and lack of adequate health infrastructure [251-253]. The emergence of *L. major* and CL is also climate-driven and associated with overpopulation of rodent reservoir hosts in the peri-domiciliary environment [254]. A further cause for the increased incidence of VL is the HIV epidemic, and in 2016, Morocco reported 12 545 *Leishmania*-HIV co-infected patients [255].

The incidence of clinical HumL is highest among children, particularly for VL, and there are substantial variations among countries.

Since the 1940s, the treatment of VL and disseminated CL has relied on the systemic administration of leishmanicidal antimonial drugs, including meglumine antimoniate and sodium stibogluconate, and to a lesser extent amphotericin B, which was first marketed in the 1980s. Less toxic and more expensive liposomal amphotericin B formulations, miltefosine and injectable paramomycin, have only been recently introduced in northern Africa and are often used as a second option in patients that do not respond to antimonials. Treatment of localised CL includes intralesional application of meglumine antimoniate, paramomycin ointments, cryotherapy and thermotherapy [254,256-262].

Integrated national control programmes are present in CL endemic areas, incorporating passive case surveillance, treatment of clinical cases and one or more of the following actions: vector control including insecticide (synthetic pyrethroids) fogging; indoor residual spraying and treated bed nets, and reservoir host population reduction. The latter includes removal of Chenopodiaceae plants, the strict diet of *P. obesus*, destruction of *Meriones* spp. burrow systems by deep ploughing and use of rodenticides [15]. Trials to evaluate the effectivity of CL control actions in Algeria, the most affected country in northern Africa, have revealed efficacies ranging between 20% and 80% [263]. Successful control was achieved following coordinated actions against vectors and reservoir hosts, with active involvement of the community.

Status of leishmaniases in Morocco

Human leishmaniases have been notifiable since 1999 and no information on the status of animal leishmaniases was found. A national control programme has been in place since 1997, with national guidelines updated in 2010. This incorporates integrated surveillance, indoor residual spraying and reservoir host population reduction. Case treatment in the national medicine list in 2014 and 2015 includes meglumine antimoniate and is free of charge [32,264].

Human leishmaniases

Between 1997 and 2018, 80 299 leishmaniases cases were reported, the great majority being CL cases [255,265]. In 2014 and 2015, Morocco notified 2 555 and 2 809 CL cases, respectively, with 81% in 2014 and 66% in 2015 caused by *L. tropica* [32,264]. The number of VL cases notified was 86 cases in 2014 and 83 cases in 2015 [32,264]. Imported cases represented a small fraction of the VL cases: 1% in 2014 and 2.2% in 2015. No CL cases were imported. The median annual VL and CL incidence per 100 000 population (incidence thereafter) according to data from the WHO GHDR is shown in Table 1 [32]. The incidence of VL cases, mostly autochthonous, gradually decreased from 0.51 in 2005–2008 to 0.26 in 2013–2016 and was 0.27 in 2017–20. In contrast, CL incidence fluctuated, and was lowest (7.90) in 2013–2016 and highest (17.05) in 2017–2020 (Table 1).

According to the 2015 WHO-CP, the age distribution of VL cases in Morocco in 2015 was as follows: 67% of the cases were below five years of age, 18% of the cases were aged 5 to 14 years and 14% of the cases were above 14 years of age [264]. The age distribution of CL cases in Morocco in 2015 caused by *L. tropica/L. major* was as follows: 31–41% of the cases were under five years of age, 30–31% of the cases were aged 5 to 14 years and 30–38% of the cases were over 14 years. In Morocco, 39% of the VL and 56% of the CL cases were female.

Traditionally, *L. major* foci are concentrated in the arid east and south-east of Morocco, in the foothills of the Anti-Atlas and High Atlas Mountain range. *Leishmania tropica* is prevalent in the semi-arid central and western slopes of the Atlas Mountains, from Azilal in the centre up to Essaouira in the west and Agadir-Guelmim in the south, with pockets also found in the northern Riff provinces. *Leishmania infantum* is the predominant species in the north, with Taounate, Taza, Chefchaouen and Al Hoceima registering the highest incidence in the 1990s.

However, species distribution and associated clinical forms have expanded over the last 15 to 20 years and infections have now been described in most parts of the country (Figures 2–5 and 8), and outbreaks of CL affecting hundreds or thousands of people in rural and urban areas are periodically reported. Visceral leishmaniasis has widened its distribution in the centre of Morocco (Figure 3), with the Fez-Boulemane provinces registering the second highest number of cases in 2007, and CL outbreaks by *L. tropica* and *L. major* reported from previously non-endemic areas in the south-east and south-west of the country, respectively (Figure 4) [253,255,266-270]. Incidence of CL peaked in 2010–2011, prompting the reactivation of the national control programme between 2010 and 2016, based on active screening, treatment of clinical cases and action against vectors, including indoor residual spraying and reservoirs of infection [264,271].

Animal leishmaniases

Few leishmaniases studies were reported in Morocco between 2009 and 2020 and the available spatial distribution of animal leishmaniases is patchy (Figure 5). Fellah et al. [272] performed a CanL epidemiological study involving 61 dogs in Fez, 52 attending a clinic and nine strays, some with symptoms, and 25% were IFAT seropositive (1/100 titre) and 9% RICT positive.

A 3% prevalence of *L. tropica* infection was reported in dogs from the southern Settat province, based on a PCR analysis of hair samples [273]. A clinical and serological study of four provinces of southern Morocco in 2004–2007 by Boussaa et al. (2014), highlighted the presence of CanL infection in southern regions, believed until then to be free of the disease: 20% (48/243) of the dogs examined displayed clinical signs compatible with CanL [274].

In a study involving 197 rodents from southern Morocco involving PCR analysis of tissue samples, *Leishmania* spp. was detected in 18 animals including six (8%) *Rattus*, 11 (20%) *Mus musculus* and one (11%) *R. norvegicus*. *Leishmania infantum* was found in rats and mice and *L. tropica* was also found in mice [275].

Sand fly infections

In the study by Ajaoud et al. [276] in Essaouira, *L. tropica* was found in three of 123 (2%) *P. sergenti* females, while in southern Morocco *L. tropica* was detected by PCR in five of 184 (2.7%) *P. sergenti* females [273]. In Azilal province in the centre of Morocco, 965 female *P. sergenti* were screened for *L. tropica* presence using PCR, resulting in a positive rate of 5.7% (55 positive sandflies) [277]. In a study carried out by Es-Sette et al, on a mixed foci of CL and VL in northern Morocco, three pools of *P. longicuspis* (0.26%) and four pools of *P.sergenti* (1.44%) were infected with *L. infantum and L. tropica*, respectively [278]. An overall minimum *L. infantum* infection rate of 2.51% (23 of 39 *P. longicuspis* pools) and 7.27% (four of four *P. perniciosus* pools) were also found in Taza province [279].

Status of leishmaniases in Algeria

In the 2000s, Algeria was the second most important focus of CL worldwide, after Afghanistan. Leishmaniases are notifiable, a surveillance programme has been in place since 1985 and a national control programme began in 2006, with national guidelines updated in 2010. The programme includes indoor residual spraying, but not reduction of the reservoir host population [17,280].

Human leishmaniases

On average, there were 44 050 CL cases annually in 2004–2008; under-reporting was considered mild [17]. These figures contrast with the annual average of 8 276 CL of cases between 2006 and 2018 mentioned by Kardjadj et al. [281], and the 5 423 CL cases in 2014 reported in the WHO-CP [280]. Based on the WHO-GHDR dataset, the median annual incidence of CL cases decreased from 33.53 in 2005–2008 to 17.90 in 2013–2016, before increasing to 26.03 in 2017–2020 [32].

The average annual number of VL cases in 2004-2–08 was 111, with mild under-reporting [17]. For the period 2006–2018, Kardjadj et al. [281] reported an average annual number of VL cases ranging between 30 and 93. Based on WHO-GHDR data, VL incidence decreased from 0.33 in 2005–2008 to 0.09 in 2017–2020 (Table 1) [32].

In Algeria, 89% of 71 VL cases diagnosed between 1998 and 2009, were below 14 years old and 61% were males; they were treated with meglumine antimoniate and 5% died [256].

Traditionally, the Tell Atlas Mountains separated the southern *L. major* and *L. tropica* area from the northern *L. infantum* area but, as elsewhere in North Africa, leishmaniases have expanded since the 1980s (Figures 8 and 9). The most active *L. major* foci are in the central Algerian provinces of Biskra, M'sila, and Adala, and new foci include the neighbouring provinces of Batna, Bechar, El Oued and Ghardaïa, Bordj Bou Arrer [254,263,282-286]. Cutaneous leishmaniasis cases by *L. tropica* were also reported in Ghardaïa [250,287], Tipaza [288] and Annaba [289] in northern Algeria (Figures 4 and 9).

Leishmania infantum infections are reported mainly from the northern Algerian province of Algiers and the Kabylia region (Tizi Ouzou, Bejaia, part of Bouia Boumerdes, Jijel, Setif and Bordj Bou Arreridj), although it is now present all along the northern fringe [254,256,262,286,289,290] (Figure 2). Cases have also been described in the central province of Biskra [289] and in the Saharan province of Tamanrasset [291].

Animal leishmaniases

Relatively few studies have been identified on animal leishmaniasis in Algeria.

Canine leishmaniases seroprevalence in randomly selected household dogs in northern Algeria in 2008–09 ranged from 27% to 47% by IFAT and between 8% and 36% by direct agglutination test, and a Bayesian estimated overall prevalence ranged from 11–38%, increasing from west to east [292].

In Kabylia, CanL prevalence in symptomatic and asymptomatic dogs was 5% by PCR in blood samples, and IFAT and RICT antibodies were detected in 36% (89% of sick dogs) and 32% of dogs, respectively [293]. In another study in this region, CanL IFAT seroprevalence was 10% and ranged between 0% in the coastal area and 16% in Dra El Mizan [285].

Leishmania major MON-25 were isolated from the skin of five out of 78 *P. obesus* collected in d'El M'hir province [282]. *Leishmania major* infection investigated in 24 hedgehogs from M'Sila revealed 13% PCR prevalence in tissue samples and 29% western blot and 26% ELISA antibodies [294].

Sand fly infection

Three of 74 (4%) *P. sergenti* females from the Ghardaia collected in 2008–9 were infected with *L. killicki* [250]. In Kabylia, *L. infantum* was detected in one of 39 (3%) *P. longicuspis* females in one study [295] and 61 of 191 (32%) *P. perniciosus* and *P. perfiliewi* in a later study [285]. In Bordj Bou Arrer, *L. infantum*, *L. major* and *L. tropica* were detected in 1.1% *P. perniciosus* in 2016 and 2017 [286].

Minimum *L. infantum* sand fly infection rates in Tipaza province in the north, obtained by pooling specimens, were 0.33% for *P. perniciosus* and 2.56% for *P. perfiliewi* [296].

Status of leishmaniases in Tunisia

Tunisia has the second highest incidence of CL in northern Africa, mostly due to *L. major*. Notification is mandatory. Tunisia has had a national control programme since 1984, with national guidelines updated in 2012. The guidelines describe the integrated surveillance of cases and reservoir host population reduction, but vector control is not included. The WHO-CP for 2014 and 2015 state that meglumine antimoniate is used to treat leishmaniasis, and that it is provided free of charge [297,298].

Human leishmaniases

In 2004–2008, the average annual number of CL cases was 7 631 cases, with underreporting considered mild [17]. In 2014 and 2015, 3 368 and 6 611 new CL cases were notified, respectively [297,298]. Similarly, the average annual number of VL cases in 2004–2008 was 89 [17]. In 2014, Tunisia reported 44 and 30 new VL cases [297,298]. Table 1, displaying WHO-GHDR data, reflects the reduction in CL incidence from 57.56 in 2005–2008 to 41.72 in 2009–2012, followed by a gradual increase to 51.61 in 2017–20. In contrast, VL incidence declined from 1.08 in 2005–2008 to 0.22 in 2017–2020 [32].

In 2015, in Tunisia VL cases were mostly children under five (53% of the cases); 10% of the VL cases were aged 5 to 14 years and 37% of the cases were over 14 years. The majority of the CL cases (64%) in Tunisia in 2015 were older than 14 years; 15% of the cases were under five and 21% of the cases were aged 5 to 14 years. In Tunisia, 53% of the VL and 51% of the CL cases were female [297,298].

The Gafsa Oasis in the south-west is a historical *L. major* hotspot. In 1982, an important CL outbreak occurred in Kairouan province in central Tunisia following the construction of the Sidi Saad dam. Since then, leishmaniases have expanded and CL, predominantly caused by *L. major*, is now endemic throughout central and southern Tunisia (Figures 4 and 8) [15,299].

It is estimated that *Leishmania tropica* causes 50–150 CL cases per year and, although traditionally restricted to the Tataouine mountain range in the south-east [299], in the mid-2000s it emerged in the south-west and central provinces of Gafsa (Metaloui) and Sidi Bouzid, respectively (Figure 9) [300,301].

Visceral and cutaneous leishmaniases by *L. infantum* was traditionally endemic in the north. However, since the 1990s VL has also been reported in the eastern province of Monastir [301] and the central province of Kairouan (Figures 2 and 3) [302,303], the latter being a heterogeneous focus of both VL by *L. infantum* and CL by *L. major* [304].

Animal leishmaniases

In Gafsa, *L. tropica* was detected in gundis (*C. gundi*), and *L. major* prevalence in *P. obesus* was 25% [248]. In Tataouine, *L. tropica* prevalence in gundis was 46% [305]. In a later study, *Leishmania* spp. was detected in 44% of gundis from Tataouine and Sidi Bouzid, and 12% of them showed signs of CL [249].

A least weasel (*Mustela nivalis*) from Sidi Bouzid was found infected with *L. major* for the first time, and in the same study, the species was detected in *P. obesus* and *M. shawi* [306]. North African hedgehogs from north-west Tunisia were found to be infected with *L. major* and *L. infantum* [306].

Leishmania infantum was detected in *P. obesus* from Sidi Bouzid and in the thin sand rat *P. vexillaris* from Kebili in the south. The latter was also infected with *L. tropica* and *L. major*. Cutaneous lesions were found in 56% of *P. obesus* but not in *P. vaxillaris* [307].

Leishmania antibodies were detected in 6.7% of the equids tested in the provinces of Kairouan, Jendouba, Ben Arous and Ariana [308].

Sand fly infections

In the first report of *L. killicki* infection in Tunisia (in Tatatouine), 2.4% of female sand flies were positive by dissection [309]. Shortly afterwards, this species was also detected in *P. sergenti* in the new focus of Gafsa (Metlaoui) [300], and *L. major* was detected in *P. papatasi* [300,310] and in *Sergentomyia minuta* [310]. *L. tropica* was subsequently detected in Sidi Bouzid by PCR in 22% of *P. sergenti*, and similarly, 23% of *P. papatasi* tested positive for *L. major* in this study [311]. In Monastir, *Leishmania* DNA was detected in seven *P. perniciosus* and *L. infantum* was identified in three of them [312]. In the same region *Leishmania* PCR prevalence was subsequently 26% in *P. perniciosus*, 9% in *P. papatasi* and 11% in *P. longicuspis,* with both *L. major* and *L. infantum* DNA being detected [313]. The latter species was also detected by PCR in 13% of the sand flies in Zagouan and all those testing positive were *P. perniciosus* [314].

In Kairouan, *L. infantum*, *L. major* and *L. killicki* were detected in 8% of *Larrossius* females (*L. perniciosus*, *longicuspis* and *perfiliewi*) [304].

The minimum *L. infantum* infection rates from pooled *P. perfiliewi*, *P. perniciosus*, *P. longicuspis*, *P. papatasi* and *S. minuta* sand flies from Sidi Bouzid, estimated by PCR, were 0.3–0.9 [315,316].

Status of leishmaniases in Libya

Leishmaniasis is a mandatorily notifiable disease in humans and a national control programme for CL has been in place since 2006.

Human leishmaniases

The average annual number of CL cases in 2004–2008 was 3 540 cases, with underreporting considered mild [17]. In 2006, 7 180 cases were recorded in eight districts, with an outbreak of 3 961 cases in Musrata (Al Jufra) and the disease spread to non-endemic areas (Figures 2, 4 and 8). Following the implementation of the national control programme, CL cases dropped to 1 800 in 2008, and CL incidence in 2009 was 71 [17,280]. Based on WHO-GHDR, the median annual CL incidence decreased from 65.43 in 2005–2008, to 16.77 in 2013–2016, increasing to 44.58 in 2017–2020 (Table 1) [32].

Prevalence of CL is widespread in the north-west around Tripoli and in Gharyian province (Figure 4); 76% of cases were caused by *L. major* and 24% by *L. tropica* (Figures 8 and 9) [317,318]. Foci for *L. major* have also been reported in the north-east and central northern provinces of Al Jabar Al Akhdar and Surt, and in the centre (Al Jufra) and the south-west (Awbary). In the latter area, *L. tropica* is also present [15,261,317]. Cutaneous leishmaniasis by *L. infantum* and *L. tropica* were reported in the inland north-west province of Nalut [319] (Figures 2 and 9).

There is little information on VL caused by *L. infantum* in Libya. According to Alvar et al. [17], only three VL cases were reported during the period 2004–2008. A VL focus was reported in a group of agricultural workers in the south of Libya in the 1990s, and considered to originate from the endemic northern provinces of Tripoli and Al Jabar Al Akhdar (Figures 2 and 3) [320]. According to WHO-GHDR, median annual VL incidence rose from 0.09 in 2013–, to 0.38 in 2017–2020 (Table 1) [32].

Animal leishmaniases and sand fly infections

No data on animal leishmaniasis could be retrieved. In the sand fly survey conducted by Obenauer et al. [320] in the city of Taurgha, three of 456 DNA pools extracted from sand flies were positive for *Leishmania*, indicating a minimum estimated infection rate of 0.83% and 0.47% for *P. papatasi* and *P. longicuspis*, respectively. In Al Rabta, northwest of Libya, two of 27 *P. sergenti* females tested positive for *L. tropica* [321].

Status of leishmaniases in Egypt

There is limited recent data on leishmaniasis in Egypt. The impact of leishmaniases in Egypt seems to be much lower than in other North African countries, although CL is considered to be a growing problem. Disease notification is not mandatory and a national control programme has been in place since 1985. Active human case

detection is performed, but on a limited scale. Insecticide spraying is carried out regularly, but on a limited scale. The reservoir host population has been reduced but it is not specifically targeted for leishmaniases [17].

Human leishmaniases

Cases of CL by *L. major* and *L. tropica* are concentrated in the north of the Sinai Peninsula, bordering Palestine (Figures 5, 8, and 9) [322,323]. Prevalence may be under-diagnosed among Bedouin communities [324] and in an active case detection survey 200 new cases were identified, confirming under-reporting to a large degree [17].

Between 2004 and 2008, the annual number of CL cases was 471 [17]. The median annual CL incidence reported in the WHO-GHDR dataset gradually increased from 0.59 in 2005–2008 to 1.49 in 2017–2020 (Table 1) [32].

In 1982, an outbreak of VL by *L. infantum* affected 20 children aged 1–4-years in a rural Bedouin setting in El-Agamy, near Alexandria (Figure 3). Dogs were the reservoirs of infection and *P. langeroni* was the sand fly vector. It was the first VL recorded in Egypt for 80 years, and the last human case reported from El Agamy was in 2005 [325]. One further VL case was reported in the Suez region in 2008. Cases from Libya and Sudan may be imported regularly but go unnoticed [17]. According to the WHO-GHDR dataset, two VL cases were reported between 2005 and 2020 (Table 1) [32].

Animal and sand fly infections

A CanL study in Giza near El Agamy revealed 10% seroprevalence (Figure 5) [326].

In the study by Shehata et al. [322], in the Sinai *L. tropica* was identified in two wild rodents (*Gerbillus pyramidum flowerі*) and *L. major* in *P. papatasi* sand flies. *Meriones crassus* and *G. pyramidum* are considered to be reservoirs of *L. major*. Viscerotropic clinical signs associated with *L. tropica* were described in *G. pyramidum* from Sinai (Figure 9) [327].

Leishmania major infection was detected in 20% of rodents (*Rattus* spp. and *Gerbillus* spp.) and in 0.5% of dissected sand flies (all positives were *P. papatasi*) collected in the Sinai between 2005 and 2011 (Figure 4) [323].

3.2.3 Status of leishmaniases in the Middle East

General epidemiological features

The Middle East is endemic for the same three *Leishmania* species that are present in northern Africa: *L. major*, *L. tropica* and *L. infantum* (Figures 2, 6, 8 and 9). The relative prevalence of infection caused by these species is variable and while *L. major* remains widespread in many areas, *L. tropica* is the predominant CL species in Syria. Reservoirs of *L. major* are found in autochthonous rodent species such as members of the *Psammomys*, *Meriones*, *Nesokia* and *Rhombomys* genera [328], and rock hyraxes (*Procavia capensis*) are reservoir hosts of *L. tropica* in Israel, Palestine and Jordan. Confirmed and suspected phlebotomine vector species in countries of the Middle East include *P. papatasi* for *L. major*, *P. sergenti* and *P. arabicus* for *L. tropica*, and *P. alexandri, P. balcanicus*, *P. galilaeus, P. halepensis, P. kandelakii, P. major* complex species, *P. perfiliewi* and *P. syriacus* for *L. infantum* [29].

The risk factors for leishmaniases described for northern Africa are similar for most of the Middle East, and the ongoing armed conflict in Syria and Iraq has had a significant effect on the epidemiology and control of leishmaniases in the area since 2011.

Status of leishmaniases in Israel

As an affluent country with strict border control, poverty-related risk factors and immigration of infected people are not major risk factors, but new constructions in sand-fly-endemic areas have been associated with outbreaks and leishmaniases are considered to be emerging diseases [329]. Disease notification is mandatory in humans and dogs. A national control programme for HumL has been implemented and national guidelines, which were updated in 2016, include integrated surveillance and reduction of reservoir host populations, but no vector control. The PCR test has replaced microscopy for case diagnosis [22]. Drugs listed in the national medicine list in 2016 were liposomal amphotericin B and sodium stibogluconate [330].

Human leishmaniases

Gandacu et al. [329] reported 2 061 CL cases between 2001 and 2012, and an annual average of 170 human CL cases was notified by the Ministry of Health for the period 2004–2008. In 2016, the country notified 242 new CL cases (WHO Israel-CP, 2016). Visceral leishmaniases was much less prevalent, with two cases annually between 2004 and 2008 and one VL case in 2016 [330]. Based on data from the Israeli government, the mean annual incidence of CL increased from 2.41 in 2004–2008, to 4.2 in 2014, decreasing to 2.81 in 2015–18. Similarly, VL incidence rose from 0.02 during the period 2004–2008, to 0.05 in 2014, decreasing to 0.01 by 2015–18. According to data from the WHO-GHDR, the median annual incidence of CL in 2005–2008 was 11.00, decreasing to 3.51 in 2009–2012, and to 1.94 by 2017–2020. As for VL, the median annual incidence ranged between 0.006 for the period 2017–2020 to 0.30 in 2013–2016 (Table 1) [32].

Cutaneous leishmaniasis is found throughout the country (Figure 4) but *Leishmania* spp. distribution is heterogeneous. *Leishmania major* is endemic in large parts of southern Israel and the Jordan Valley where *P. obesus* is the main reservoir host (Figure 8) [331]. A large increase in CL cases was reported in the southern district during the period 2007–2013, with a cluster of cases in the north-west of the district, raising incidence from six to 43 cases per 100 000 inhabitants [332]. A new focus of *L. major* was detected in 2006 in the north-east near the Jordan river, associated with the previously unknown reservoir hosts, Tristram's jirds (*Meriones tristrami*) and social voles (*Microtus guentheri*) (Figure 8) [333].

Leishmania tropica is emerging in populated areas of the Galilee region in northern Israel and the Judean Desert in central Israel due to encroachment of rock hyraxes upon human habitation (Figure 9) [334-336]. The sand fly vectors are *P. sergenti* in central and northern Israel, and *P. arabicus* in parts of northern Israel.

A study of CL in the Israeli army, including records from three decades, showed striking differences in CL the seasonality patterns and incidence rates for *L. major* and *L. tropica* between military personnel and civilians. The average monthly rates in soldiers varied from 0.8/100 000 cases in June to 10/100 000 in December [337].

Human VL by *L. infantum* is sporadically found throughout central and northern Israel (Figure 2 and 3). Genotyping studies of human and canine strains revealed two separate populations – one occurring only in central Israel and the other in central Israel and Palestine[5] [338]. In another study, *L. infantum* strains from Israel and Palestine were found to be distinct from European strains. Two separate populations were found, each containing parasites from different areas of Israel and from Palestine, suggesting similar disease dynamics in Israel and Palestine [339].

Animal leishmaniases

An outbreak of *L. infantum* in dogs and cats was reported in a common facility in northern Israel, with 42% of dogs and 79% of cats found to be seropositive and/or PCR positive in blood samples [340] (Figure 2). Other reports described dogs infected with *L. major* [341] and *L. tropica* [342], both successfully treated with allopurinol. A subsequent study demonstrated significant serological cross-reactivity in serum samples from dogs infected with *L. major*, *L. tropica* and *L. infantum* tested using ELISA and rk39-RICT [343].

Leishmania infantum DAT seroprevalence in 338 horses, mainly from northern and central Israel, was 1.4% [344].

Leishmania tropica was detected in hyraxes with 58% of blood samples testing positive using PCR and 80% using serological western-blot analysis [336]. This species was also detected by PCR in 8% of tissue samples from golden jackals and red foxes, suggesting their potential role as reservoirs of *L. tropica* infection in Israel [345].

Sand fly infections

In the Negev region, *L. major* was detected in 10% of 807 pools, each containing 100 to 400 female *P. papatasi* [346].

Status of leishmaniases in Palestine

Leishmaniases are notifiable in humans only, and *L. major*, *L. tropica* and *L. infantum* are endemic [346]. There is a control programme in place for *L. infantum*, based on treating dogs and euthanising those that cannot be treated [22].

Human leishmaniases

The annual average number of CL cases reported during the period 2004–2008 period was 218, with under-reporting considered to be mild [17]. Between 2007 and 2018, 2 672 CL were reported from the West Bank, and no data are available from Gaza [347]. In the WHO-GHDR dataset, there are no CL cases and two VL cases reported [32].

A study of CL between 1994 and 2015 revealed that 58% of cases were caused by *L. major* and 42% by *L. tropica*, and cases peaked in 1995, 2001, 2004 and 2012. Cases from the Jericho district in the Central Jordan Valley were caused mainly by *L. major*, and *L. tropica* was the predominant species among the approximately 30% cases from other West Bank districts (Figures 4, 8, and 9). The fat sand rat, *Psammomys obesus* is endemic in the Central Jordan Valley due to the availability of its main source of food, the *Atriplex* species of plant [348].

An annual average of five VL cases was recorded in the period 2004–2008, with underreporting considered to be mild [17]. The total number of human VL cases reported in the West Bank between 1990 and 2017 was 343 cases and the mean annual incidence was 0.73 cases [349]. Incidence of VL during the period 1990–2017 was highest in the northern district of Jenin (2.17) and in the southern districts of Hebron (1.0) (Figures 2 and 3) [349]. A previous VL study in Hebron between 1993 and 2007 reported 29 VL cases, all children, raising incidence in the district to 3.02 people. Putative vectors were *P. syriacus* and *P. tobbi* [350].

Animal leishmaniases and sand fly infections

Canine leishmaniasis seroprevalence and PCR prevalence in blood samples from dogs across the West Bank area was 8% and 14%, respectively, and 17% tested positive using one or both techniques (Figure 5). Prevalence was highest in Jenin (25%) and Hebron (28%) [351].

[5] This designation shall not be construed as recognition of a State of Palestine and is without prejudice to the individual positions of the Member States on this issue.

No studies reported *Leishmania* infection rates in sand flies.

Status of leishmaniases in Jordan

Leishmaniases are mandatorily notifiable in humans and animals, and there is no national control programme. Endemic species include *L. major* and *L. tropica* and human infections by *L. infantum* are very rare, with no cases reported during the period 2004–2008 [17] or 2009–18. However, CanL by *L. infantum* is considered endemic [22].

Human leishmaniases

The average annual number of CL cases in the period 2004–2008 was 227, and under-reporting is considered mild. However, between 2010 and 2016, 1 243 CL cases were reported, associated with the arrival of refugees from neighbouring Syria [328]. In a nationwide serological study (rK39 and ELISA) between 2015 and 2016, seroprevalence was 2.5% and 11% respectively in the Madaba province [352].

Leishmania major, the predominant entity, is endemic in the Jordan Valley, and outbreaks of CL involving 100–200 cases were reported every year between 2004 and 2008: in Aqaba (2006 and 2007), North Agwar (2008) and South Shuneh (2004 and 2005) (Figures 4 and 8) [17].

Leishmania tropica is more frequent in northern Jordan (Figure 9) [328,353]. A CL outbreak affecting 183 people was reported for the first time in the north of the Jordanian Valley between April 2008 and May 2009, with *L. major* was detected in 53/56 patients tested, and *L. tropica* in the remaining three [354].

The annual incidence of CL per 100 000 population between 2004 and 2008 was 3.83 [17]. In 2012, the incidence was 1.3, increasing to 2.8 cases in 2016 as a result of the influx of Syrian refugees [355]. There is evidence that most infections were acquired in Syria, where *L. tropica* is the predominant species [356]. Based on WHO-GHDR data, the median annual CL incidence was 3.37, 1.96, 2.93 and 1.12 in 2005–2008, 2009–12, 2013–2016 and 2017–20, respectively, and a large number of cases were imported (Table 1). In contrast, eight VL cases were reported between 2013 and 2020 [32].

Animal leishmaniases and sand fly infections

No studies reported *Leishmania* infections in animals and sand flies in Jordan.

Status of leishmaniases in Lebanon

Leishmaniases are notifiable. Autochthonous cases are sporadic and caused by *L. infantum* and *L. major*. There is no national control programme, but rodent control is regularly carried out [17].

Human leishmaniases

Lebanon reported no CL or VL cases in the period 2004–2008 [17]. Between 1926 and 1964, the country had recorded around two VL cases annually.

Atypical systemic leishmaniases was reported in 31 of 160 immunosuppressed patients, 85% were 0–12 years-old and 48% came from the Akkar district in northern Lebanon, the site of a VL outbreak in 1999–2000 (Figures 2 and 3) [357].

In an epidemiological study in 81 000 randomly selected Lebanese citizens between 1993 and 1997, CL prevalence was 0.18% in rural areas and 0.41% among urban people; 2.5% of these citizens tested positive with the Leishmanin skin test and 1% tested positive using ELISA (rk39); two cases of VL were diagnosed. Unexpectedly, *L. infantum* was the cause of many CL cases [358].

Since 2013, Lebanon has experienced a surge of CL incidence following the mass influx of Syrian refugees [359-361]. The number of annual CL cases reported rose from 0–6 cases between 2000 and 2012, to 1 033 cases in 2013, 97% of which were in Syrians, the rest being among Lebanese citizens and Palestinian[6] refugees. Most Syrian refugees were infected with *L. tropica* [356]. According to WHO-GHDR dataset, the median annual CL incidence was below 0.07 during the period 2005–2012, increasing to 3.83 in 2017–2020 before peaking at 9.49 in 2013–2016; with the great majority of cases imported (Table 1). Two VL cases were reported between 2013 and 2020 [32].

Animal leishmaniases and sand fly infections

There are no reports of *Leishmania* infection in animals and sand flies in Lebanon.

Status of leishmaniases in Syria

There were more than 80 000 reported CL cases in 2015 and 2018, and due to massive population displacement, high incidence is no longer restricted to the Aleppo region in the north-west [362]. Furthermore, lack of control programmes, health facilities and drugs to treat clinical cases and malnutrition have contributed to the emergence of leishmaniases in this country. Millions have fled into neighbouring countries, especially Jordan, Lebanon and Turkey, and refugee camps in these countries are leishmaniases hotspots where concentrations of clinical cases are housed in inadequate accommodation, with poor sanitation, an absence of clean water and an environment that favours sand fly vector proliferation [363].

[6] This designation shall not be construed as recognition of a State of Palestine and is without prejudice to the individual positions of the Member States on this issue

3.2.4 Status of leishmaniases in Turkey and the Caucasus

Status of leishmaniases in Turkey

Leishmaniases notification is mandatory in humans. Autochthonous species include *L. tropica*, *L. major* and both *L. donovani* complex species, *L. infantum* and *L. donovani s. s.*, affecting humans and animals with variable distribution (Figures 2 and 7-9). There is a national control programme for *L. major* and *L. tropica* that includes screening, testing of immigrants and the use of insecticides in the peri- and intra-domestic environment. The national control programme is part of the 'One Health' Turkish Zoonotic Diseases Action Plan (2019–2023) organised by the Turkish National Committee for Zoonotic Diseases, with the participation of the Ministry of Agriculture and Forestry and the Ministry of Health [22].

At the cross-roads between the rest of Europe, the Middle East and the Caucasus, Turkey has the greatest vector diversity in the study zone. These vectors include *P. sergenti* for *L. tropica*, *P. papatasi* for *L. major* and *P. alexandri, P. balcanicus*, *P. halepensis, P. kandelakii, P. major s.l, P. mascittii, P. perfiliewi*, *P. simici, P. similis* and *P. tobbi* for *L. infantum* [18].

The country has a large network of technical and scientific groups performing clinical and epidemiological research on human and animal leishmaniases that make use of the wide spectrum of serological and molecular diagnostic techniques. Nevertheless, diagnosis in primary health centres relies strongly on classical methods based on epidemiological information, identification of typical clinical symptoms, the detection of parasites by microscopy and treatment response.

Human leishmaniases

Between 2003 and 2007, Turkey reported an average of 29 annual VL cases. There were 2 465 annual CL cases, and under-reporting is considered to be mild for both clinical forms [17]. The number of cases reported in the 2014, 2016 and 2018 WHO-CP [364,365], were 22, 23 and 14 new VL cases, respectively. Similarly, there were 3 997, 2 563 and 2 392 CL cases. Imported cases represented 38% of the VL cases in 2016 and between 35% and 58% of the CL cases in 2014, 2016 and 2018. According to the WHO-GHDR dataset, the median annual CL incidence was 2.45 in 2005–2008, increasing to 4.60 in 2013–2016, and decreasing to 2.91 in 2017–2020. A large proportion of cases were imported, particularly between 2013 and 2020 (Table 1). Similarly, for VL incidence ranged from 0.04 to 0.05 between 2005–2008 and 2017–2020 (Table 1) [32].

The age-specific percentages of VL cases reported in 2014, 2016 and 2018 [364-366] ranged from 0–32% for those <5 years old, 22–30% for 5–14 years old and 42–68% for those >14 years. Similarly, for CL these ranges were 0–18% for those <5 years old, 33–34% for those aged 5–14 years and 48–64% for >14 years old. *Leishmania*-HIV coinfections are infrequent. First-line treatment for VL is with antimonials – cure rate 95% - and second-line with liposomal amphotericin B [1]. In 2016, no deaths were reported among cases and for 2014 and 2018 no information was provided on deaths [364-366].

Of 81 provinces in Turkey, CL and VL has been reported from 32 NUTS3 sub-divisions (Table 25) (Figures 3 and 4) [367-373], and VL from 28 NUTS3 (Figure 4) [367,374-379]. The NUTS3 sub-divisions where CL cases were most common, in order of frequency, were Şanlıurfa, 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 reported from 30, 25, 11 and 10 NUTS3 sub-divisions, respectively, and all four species were reported from Adana, Antalya, Diyarbakır, Hatay, Manisa, Mardin and Sanliurfa (Table 25).

Six studies investigated the prevalence of leishmaniases in randomly selected humans between 2006 and 2013, two focused on CL and four on VL (Table 26). The prevalence of CL was 4% in children and adults in Adana [380] and 0.3% in children in Sanliurfa [381], assessed by clinical examination to detect cutaneous lesions, followed by identification of amastigotes in skin scrapings from lesions using optical microscopy. The prevalence of asymptomatic *Leishmania* infection, typically associated with *L. infantum* responsible for VL, was investigated in blood donors in Istanbul [377,382], children and adults in Denizli [383] and in children in Kars [384]. Antibody prevalence in blood donors ranged between 0% and 6%, depending on the diagnostic test (ELISA, IFAT, RICT) and the IFAT positivity threshold, and was 1.2% using microculture methods in buffy coat samples.

Animal leishmaniases

Canine leishmaniases has been reported from 21 provinces in Turkey (Table 27 and Figure 5) [367,374,384-393]. Seventeen studies investigated the prevalence of CanL in randomly selected dogs from shelters, kennels and households in urban and rural areas in 18 provinces (Table 27) [374,384,386,387,390,391,393-396] using antibody serological assays - mostly IFAT (positivity threshold of 40, 64 and 128) and PCR in blood, conjunctival swabs and lymph node aspirates. IFAT seroprevalence ranged from 27% to 0% and was ≥19% in Adana, Aydin, Denizli, Eskisehir and Mersin. PCR prevalence in blood samples ranged between 2−10% and was always lower than IFAT seroprevalence in dogs tested using 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 performing parasite identification.

Leishmania prevalence in randomly selected cats was investigated in five studies, including one in the western provinces of Aydin, Izmir, Mersin and Mugla, two other studies in Izmir, one in Mersin and one in Icel (Table 27) [395,397-400]. One study in Izmir estimated prevalence in blood samples from the same cats using different techniques: 15% by IFAT (threshold of 40), 11% by ELISA and 0.5 % by PCR, which included five cats infected with *L. tropica* and one cat with a mixed *L. tropica* and *L. infantum* infection. Furthermore, in Izmir, prevalence assessed by PCR in conjunctival swabs was 5.3%, with the species being identified as *L. infantum*. In Icel, one of the blood samples from 22 (4.6%) cats tested using PCR was positive and the species was identified as *L. infantum*. No cats in Mersin had PCR-positive blood samples. Overall, blood-PCR prevalence in the study of the western provinces was 6%, including nine cats with *L. tropica* and four cats with *L. major*.

Leishmania spp. prevalence in spleen, liver and lung samples of 712 wild rodents from 30 provinces analysed by PCR was 1.12% [401]. 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.

Sand fly infections

Leishmania spp. infection rates were analysed in ten sand fly studies from ten provinces by dissection or PCR of individual or pooled sand fly specimens (Table 28) [389,396,402-406]. Infection rates in samples analysed individually ranged from 0% in specimens from Denizli and Sinop to 1.96% in *Sergentomyia dentatae* and 1.90% in *P. tobbi* from Aydin and Osmaniye, respectively. Similarly, minimum infection rates in pooled samples ranged from 0.63% in *P. papatasi* from Nigde to 5.17% in *P. neglectus* from Aydin.

General epidemiological features for countries in the Caucasus

At the time when Armenia, Azerbaijan and Georgia were part of the Soviet Union, they benefited from fully-fledged leishmaniases control programmes. The situation deteriorated following independence in the early 1990s and since then VL has re-emerged. Notification of human leishmaniases is mandatory, but under-reporting is considered high [407].

Although *L. infantum* is present in all three countries, *L. tropica* and *L. major* are reported only in Azerbaijan (Figures 2, 8 and 9). Sand fly vectors in the regions (with variable frequency and distribution) include *P. sergenti* for *L. tropica*, *P. papatasi* for *L. major* and *P. alexandri, P. balcanicus*, *P. halepensis, P. kandelakii, P. major s.l., P. perfiliewi*, *P. pernicious, P. simici, P. similis* and *P. tobbi* for *L. infantum* [18]. The reservoir host species for *L. major* in Azerbaijan is the *P. obesus*, which is endemic throughout central Asia.

Diagnosis of leishmaniases relies mostly on clinical signs and parasite identification by microscopy. More recently, antibody (IFAT, ELISA, direct agglutination test and RICT) and PCR methods have become available. Children in the age group 0−5 years account for the vast majority of cases (65−85%) [407-412] and *Leishmania*-HIV coinfections have either not been reported or are infrequent [33]. First-line treatment is with antimonials, with a mortality rate of up to 10% in Azerbaijan [33]. Notification status and availability and characteristics of surveillance and control programmes vary among the countries, as described below.

Status of leishmaniases in Armenia

The country is endemic for VL and CL by *L. infantum*. Notification of both human and animal leishmaniases is mandatory and there is a national control programme, centred on diagnosis and euthanasia of sick stray dogs and insecticide spraying against sand fly vectors [22].

Human leishmaniases

Between 1999 and 2016, 116 autochthonous VL cases were reported, and the average annual number of VL cases between 2004 and 2008 was seven, with under-reporting considered moderate [17]. The corresponding incidence for 2004−2008 was 0.22. According to the WHO-GHDR dataset, median annual VL incidence gradually rose from 0.24 during the period 2005−2008 to 0.58 in 2017−2020 (Table 1). Three CL cases, all imported, were reported during this period [32].

Clinical VL cases reported between 2012 and 2016 originated from eight of 11 districts in the country (Figures 2 and 3) and mostly from around Yerevan, Armenia's capital city in the central western part of the country, the southern district of Syunik and the northern districts of Tavush and Lori [409,410]. In 2015−2016, seroprevalence among 1 200 randomly-selected healthy children under 10 years from VL foci districts was 0.3% [410].

Animal leishmaniases and sand fly infections

Canine leishmaniases occurs in the same localities as human VL cases [410]. *Leishmania* spp. has also been detected in cats, foxes, wolves, jackals and rodents in Armenia [409,410].

There are no studies of *Leishmania* infections in sand flies.

Status of leishmaniases in Azerbaijan

Leishmaniases are notifiable in humans and animals. Endemic species traditionally include *L. infantum*, *L. tropica* and *L. major*. A national control programme and national guidelines exist and activities include the use of insecticides in dogs and in the peri- and intra-domiciliary environment, insecticide-treated bed nets, habitat destruction of rodent host species and the testing of immigrants for *Leishmania* infection [22,62].

Human leishmaniases

Between 2004 and 2008, the average annual number of VL cases was 28 and under-reporting was considered to be mild [17]. The corresponding VL incidence was 0.33. Between 2014 and 2018, 170 human VL cases by *L. infantum* were reported in 33 districts, with the highest number coming from Barda (15%), Terter (14%), Sheki (8%) and Shamkir (8%) (Figures 2 and 3) [409]. Based on WHO-GHDR data, the median annual incidence of VL ranged between 0.21 and 0.33 for the period 2005–2016 and was 0.52 in 2017–2020 (Table 1) [32].

No cases of CL by *L. infantum* have been reported since the late 1980s outbreak in Geokchay which affected 68 people [409]. The incidence of CL by *L. major* in 1990 was almost ten times higher than in 1985, and 1 340 cases of CL were registered in the period 1989–1997, decreasing to 257 cases for 1998–2009. Between 2004 and 2008, the average annual number of CL cases was 17 and under-reporting was considered to be mild [17]. The corresponding incidence for this period was 0.20. The median annual CL incidence reported in the WHO-GHDR dataset was 0.19, 0.35, 0.27 and 0.16 for 2005–2008, 2009–12, 2013–2016 and 2017–20, and all cases were autochthonous (Table 1) [32].

Zoonotic CL cases caused by *L. major* have been registered in the lowland districts of Geokchay, Agdash and Ujar since the late 1980s (Figure 8). In the 1950s, *Leishmania tropica* was responsible for over 2 000 CL cases [17]. No other reports were found which specifically mentioned this species.

Animal leishmaniases and sand fly infections

Canine leishmaniases by *L. infantum* is found in all districts where human VL occurs. In the 1980s, the prevalence of clinical cases in stray dogs in Ordubad was 18%, and IFAT seroprevalence in dogs in Jalilabad was 17% (Figures 2 and 5) [409]. In the 1960s, 2 388 wild animals were examined for *Leishmania* infection and the disease was detected in two foxes and one cat [409].

There are no reports of *Leishmania* infection in sand flies in Azerbaijan.

Status of leishmaniases in Georgia

Human and animal leishmaniases are notifiable, the country is endemic for *L. infantum* and there is a national surveillance scheme. The answers obtained from the questionnaire on the existence of a national control programme were contradictory and only the HumL questionnaire acknowledged the existence of a programme, based on the use of insecticides, treatment and euthanasia of sick dogs [22].

Human leishmaniases

Strelkova et al. [409] has described a steady increase in the number of cases since the mid-1990s. The average annual number of VL cases between 2004 and 2008 was 164, and under-reporting was considered to be mild [17]. There were 51 and 57 new VL cases reported in 2014 and 2016, respectively [412,413]. In both years, there were 12 relapses. Among these VL cases, 8% and 4% were imported in 2014 and 2016, respectively. One CL case was reported in 2015.

For the period 2004–2008 the average incidence was 3.73, for 2014–2016 it was 1.37 and for 2018 it was 1.80. In 2016, the age distribution of VL cases in Georgia was as follows: 62% of the cases were below five years of age, 10% of the cases were aged 5 to 14 years and 29% of the cases were over 14 years [412]. According to the WHO-GHDR dataset, the median annual VL incidence has gradually decreased from 4.46 in 2005–2008 to 1.20 in 2017–2020 (Table 1). For CL, incidence was highest in 2009–2012 (0.15) and no cases were reported in 2017–2020 (Table 1) [32].

Most VL cases from 1999 to 2010 were reported from Tbilisi and the vicinity, and a new focus is reported in the western city of Kutaisi (Figures 2 and 3) [408].

Antibody prevalence in healthy humans in the Tbilisi area during the mid-2000s, assessed with the DAT, was 7% [414]. In a later study, the prevalence of asymptomatic human infection in the Tbilisi and Kutaisi regions in the late 2000s estimated with the leishmanin skin test, was 15% and 7% respectively [415].

Animal leishmaniases

Clinical cases in dogs are common in areas with human cases. Seroprevalence in mostly asymptomatic stray and household dogs in the Tbilisi area (Figure 5) during the mid-2000s, analysed with rk39 RICT was 15–18% [414]. In a subsequent study (2011) in the Tbilisi area which also used the rk39 RICT, the estimated seroprevalence was 22–28% in household dogs, 16% in stray dogs and 3% in wild canids (foxes and jackals) [416].

Sand fly infections

In the Tbilisi area in 2008–10, *L. infantum* DNA was detected in 2% *P. kandelakii* and 5% *P. balcanicus* [417]. A later study in Tbilisi and Kutaisi in 2011, detected infection in 2% *P. balcanicus* and 6% *P. kandelakii* [415]. In Kvareli in 2014, 7% of infections were with *P. balcanicus* [416].

4. Discussion

This study analysed the distribution; evidence of emergence; statuary notification; surveillance and control measures; availability of diagnostic methods and treatment of human and animal leishmaniases in areas of the European Union and neighbouring countries where infection and/or vectors are present. The study was based on a review of the scientific literature, including the grey literature, published since 2009 and a questionnaire survey. Based on the number of cases reported in the WHO-GHDR dataset for all countries, the National Epidemiological Surveillance Networks of Bulgaria, France and Greece and the centralised hospital discharge databases of Italy, Malta, Portugal and Spain, we concluded that in the last 10−15 years the incidence of CL has significantly decreased in Georgia and Israel, increased in Spain and France and fluctuated greatly in the Middle East and Turkey, the latter being the result of a massive influx of refugees from Syria, Iraq and Afghanistan. Incidence of VL increased significantly or marginally in Armenia, Azerbaijan, France, Greece and Libya and decreased significantly in Albania, Algeria, Croatia, Georgia, Morocco and Tunisia. Moreover, there is evidence of leishmaniases emerging on a sub-national scale in endemic countries such as Spain, Italy and Greece and in previously non-endemic countries such as Romania. In addition, based on the questionnaire survey addressed to the public health and veterinary authorities of Albania, Algeria, Armenia, Austria, Azerbaijan, Cyprus, France, Georgia, Italy, Malta, Montenegro, North Macedonia, Romania, Spain and Turkey, leishmaniases are emerging diseases in the whole or parts of all these countries.

The following factors were identified as possible bias of the above analysis of leishmaniasis incidence over time: differences between and within countries over time with respect to the sensitivity of their surveillance systems; the leishmania notification status (mandatory versus voluntary); the quality of data from different sources; differences in diagnosis capacity and clinicians' awareness (among countries, and within a country at different periods in time).

The assessment of emergence was based on data from the sources mentioned above and the opinion of the public health and veterinary authorities. As emergence can be observed at the sub-national level, for a more accurate assessment, quantitative data are required on the sub-national incidence of autochthonous leishmaniases. Such data would also make it possible to contrast and improve the precision of the maps in the present report, which were created using cases reported in the scientific literature, and not all articles distinguish autochthonous and imported cases.

Few countries implement specific surveillance and control programmes targeting both animal and human leishmaniases, suggesting it is not a priority for health authorities. Very little information is available on the websites of national authorities; no information was found on the establishment of control programmes or the coordination of surveillance activities. This suggests that the EU and neighbouring countries should consider strengthening their communication on the surveillance and control of the disease, where relevant.

Rapid intervention to eliminate exposure to infected animals in the domestic environment is essential to reduce the transmission risk of zoonotic *Leishmania* spp. to other animals and humans. Mandatory reporting of canine leishmaniasis would also allow the collection of more precise information on disease distribution and to estimate its actual impact. Leishmaniases in the EU and its neighbour countries are a transnational problem, affecting not only endemic countries but also non-endemic central and northern European countries, which see a high number of imported cases [46,49,61,67-73,418]. In those non-endemic countries where competent vectors are present, surveillance, prompt treatment of cases and implementation of other control measures would reduce the likelihood of disease establishment.

The review highlights some gaps in the reporting of leishmaniases. There is a high variability in number of cases recorded in the different datasets - the hospital discharge records obtained from two countries suggest that the number of human cases notified to WHO (WHO-CP and WHO-GHDR) is largely an underestimate. Under-reporting is probably particularly severe for CL since most cases do not require hospitalisation.

Similarly, the number of leishmaniasis cases among animals is under-reported. A published survey among Spanish and French veterinary clinicians highlighted that a large proportion of veterinarians are not reporting CanL [201]. In addition, under-reporting is exemplified by the gap in data observed on the WOAH website, despite the disease being mandatorily notifiable to the WOAH. Leishmaniases is not in the current EU list of notifiable diseases for humans and animals, hence the absence of data available from EU institutions (i.e. ECDC and EFSA).

In general, integrated leishmaniases control measures involving humans, domestic animals, wildlife and sand fly vectors are rare and limited to the control of outbreaks. Consideration could be given to widening this approach to control leishmaniases more generally, through coordination of public health, veterinary, entomology and environmental services to design and implement integrated leishmaniases control strategies, which include active community participation.

This review also highlights the use of a very wide range of serological and molecular tests and protocols for the diagnosis of leishmaniases, which makes it challenging to compare published studies. A description of the diagnostic techniques is provided in the WOAH's Manual of Diagnostic Tests and Vaccines for Terrestrial Animals [419]. Having agreed and adopted gold standard diagnostic methods would facilitate comparison of results and therefore a better

estimation of the epidemiological situation. Moreover, based on the questionnaire replies and the national governmental web-pages retrieved, only a minority of countries have diagnostic and treatment guidelines. WHO has published a manual on case management and surveillance of leishmaniasis in the WHO European Region [420] that could serve as a basis for the development of national guidelines for public health. In addition, given the interrelated nature of the disease's epidemiology in animals, humans and vectors, the development of intersectoral guidelines for the prevention and control of leishmaniases in the EU and its neighbouring countries could be considered.

Sensitive molecular diagnostic methods (i.e. PCR assays and DNA sequencing) and liposomal amphotericin B and miltefosine treatments are expensive and not widely available in the less well-resourced countries. Molecular diagnostic tests are necessary for a better understanding of leishmaniases epidemiology. Wider use of liposomal amphotericin B and miltefosine for HumL treatment is needed to reduce treatment failures and side effects caused by more toxic antimonial compounds, as well as to avoid the risk of *Leishmania* spp. developing resistance. To reduce the risk of treatment resistance, different first-line treatments should be selected for HumL and AniL.

5. Conclusions

Leishmaniases remain widespread and under-reported in the southern part of Europe and beyond. Measures for leishmaniases prevention and control, access to valid diagnostic methods and guidelines, and access to effective treatments vary considerably between countries, and in some areas these appear to need strengthening. This variation, and in particular, the lack of resources in some countries or regions, could have important disease implications including increased incidence in the EU and neighbouring countries; unnoticed spread of *Leishmania spp*. into new areas; increased treatment failure and development of resistance to treatments.

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