Leishmaniosis in Rodents Caused by Leishmania infantum: A Review of Studies in the Mediterranean Area

M. Magdalena Alcover*, M. Cristina Riera and Roser Fisa

Section of Parasitology, Department of Biology, Health, and Environment, Faculty of Pharmacy and Food Science, University of Barcelona, Barcelona, Spain

Leishmaniosis infection begins when a phlebotomine sand fly vector inoculates pathogenic protozoan parasites of the genus Leishmania into a mammalian host. In the case of Leishmania infantum, the domestic dog is considered to be the main parasite reservoir, and canine leishmaniosis (CanL) has a high mortality rate in untreated dogs. Hundreds of cases of human leishmaniosis (HL) are reported in the world each year, the incidence in Europe being relatively low. Leishmaniosis control is primarily focused on the dog, combining methods that prevent sand fly bites and boost host resistance to infection. However, these measures are only partially effective and new solutions need to be found. One of the main factors limiting CanL and HL control is the existence of a sylvatic Leishmania transmission cycle that interacts with the domestic cycle maintained by dogs. It is suspected that the main reservoir of infection in wildlife are rodents, whose expansion and rapid population growth worldwide is increasing the risk of human and zoonotic pathogen transfer. The aim of this review is therefore to analyze reports in the literature that may shed light on the potential role of rodents in the leishmaniosis transmission cycle in the Mediterranean area. Following the general methodology recommended for reviews, six databases (Google Scholar, Ovid, PubMed, Science Direct, Scopus and Web of Science) were explored for the period January 1995 to December 2020. The results extracted from 39 publications that met the established inclusion criteria were analyzed. It was found that 23 species of rodents have been studied in nine countries of the Mediterranean basin. Of the 3,643 specimens studied, 302 tested positive for L. infantum infection by serology, microscopy and/or molecular techniques.

Keywords: Leishmania infantum, zoonosis, rodentia, reservoir, wildlife, Mediterranean basin

INTRODUCTION

Leishmaniosis is a parasitic vector-borne disease caused by Leishmania spp. affecting humans and other mammals. In Europe, leishmaniosis (caused mainly by Leishmania infantum) is an emerging zoonosis, with 700 new cases appearing annually (1). Of the four Leishmania species present in the Mediterranean basin, L. infantum is predominant and the causative agent of the human form of visceral (VL), cutaneous (CL), and mucocutaneous leishmaniosis (MCL). The others are Leishmania major (North Africa and the Middle East; CL), Leishmania tropica (Greece, Turkey, the Middle East and North Africa; CL), and Leishmania donovani (Cyprus; VL and CL) (2, 3).
FIGURE 1 | (A) Percentage of each type of study (review, clinical or epidemiological); (B) percentage of studies published in each country; (C) percentage of studies published in each geographical area.
TABLE 1 | Median (rank) of studied rodents and the prevalence of infection in each country.

| Country | Number of rodents | P-value | Number of infected rodents | P-value | Prevalence of infection | P-value |
|---------|------------------|---------|----------------------------|---------|-------------------------|---------|
| Algeria | 3 (-)            | 0.150   | 0 (-)                      | 0.369   | 0.00 (-)                | 0.131   |
| Cyprus  | 494 (-)          |         | 36 (-)                     |         | 7.29 (-)                |         |
| Spain   | 37 (7–150)       |         | 9 (1–29)                   |         | 29.59 (0.67–88.89)      |         |
| Greece  | 57 (16–97)       |         | 14 (1–19)                  |         | 16.53 (6.25–26.80)      |         |
| Iran    | 108 (15–566)     |         | 1 (0–60)                   |         | 0.27 (0.00–30.93)       |         |
| Morocco | 197 (-)          |         | 16 (-)                     |         | 8.12 (-)                |         |
| Portugal| 30 (-)           |         | 9 (-)                      |         | 30.00 (-)               |         |
| Tunisia | 72 (-)           |         | 26 (-)                     |         | 36.11 (-)               |         |
| Turkey  | 432 (-)          |         | 5 (-)                      |         | 1.16 (-)                |         |

P-value ≤ 0.05 is considered as statistically significant.

TABLE 2 | Median (rank) of studied variables according to the geographical area.

| Area               | Number of rodents | P-value | Number of infected rodents | P-value | Prevalence of infection | P-value |
|--------------------|-------------------|---------|----------------------------|---------|-------------------------|---------|
| Southern Europe    | 37 (7–494)        | 0.168   | 9 (1–36)                   | 0.150   | 26.80 (0.67–88.89)      | 0.020   |
| North Africa       | 72 (3–197)        |         | 16 (0–26)                  |         | 8.12 (0.00–36.11)       |         |
| Middle East        | 117 (15–566)      |         | 3 (0–60)                   |         | 0.72 (0.00–30.93)       |         |

P-value ≤ 0.05 is considered as statistically significant.

These *Leishmania* species are capable of spreading to new geographical areas that have sufficient numbers of suitable sand fly vectors and favorable ecological conditions (4).

In the Mediterranean basin and surrounding areas, where *L. infantum* is endemic (5–8), dogs are currently considered to be the main reservoir. Thanks to the application of molecular tools and serology, *Leishmania* has been detected in clinically healthy and seronegative mammals, not only dogs but also other domestic/peri-domestic and wild mammal species, including rodents (9–13). The long list of potential reservoir hosts suggests that *Leishmania* can be transmitted to a diverse range of mammals through sand fly bites and that wild mammals can suffer frequent and non-specific infection (14). The abundance and widespread distribution of rodents, together with their longevity, which allows them to survive an entire sand fly season, makes them likely candidates for infection with *Leishmania* species, including *L. infantum* (15). Furthermore, rodents are known to remain asymptomatic carriers for very long periods (16–19). Consequently, it can be hypothesized that rodent populations, as well as other wild animals, can maintain the permanent circulation of the parasite in an endemic area.

Many interacting host species fulfill the criteria that define a reservoir of *Leishmania* (abundance; attracting and infecting sand flies; evidence of long-term infection at the individual or species level) (20). Nevertheless, their categorization as primary, secondary, or accidental reservoirs depends on local ecological and epidemiological conditions. Although, it has not been demonstrated that rodents (and wildlife in general) act as a reservoir for *Leishmania*, some species of rodents are known to contribute to maintaining the circulation of *L. infantum* in certain areas of southern Europe (11). Studies employing xenodiagnosis could help to determine the role of wildlife in the current epidemiology of leishmaniosis, as demonstrated in an outbreak in Fuenlabrada (Madrid) (21), where this approach incriminated lagomorphs as the source of human infection.
FIGURE 3  | (A) Captured rodents. (B) Infected rodents. (C) Prevalence of infection among different rodent families.
TABLE 3 | Global prevalence and IC\textsubscript{95} of infection in each species and subfamily.

| Subfamily       | Species                  | Global prevalence of infection | IC\textsubscript{95} | P-value | P-value |
|-----------------|--------------------------|-------------------------------|----------------------|---------|---------|
| Arvicolinae     | Microtus arvalis         | 0.0%                          | –                    | –       | <0.001  |
| Callosciurinae  | Funambulus pennantii     | 0.0%                          | –                    | –       | –       |
| Cricetinae      | Cricetus migratorius     | 15.0%                         | 3.93–26.07%          | <0.001  |         |
|                 | Mesocricetus auratus     | 75%                           | 28.4–97.2%           |         |         |
| Gerbillinae     | Gerbillus campestris     | 2.98%                         | 2.08–3.88%           | <0.001  |         |
|                 | Meriones crassus         | 0.0%                          | –                    | –       | –       |
|                 | Meriones hurianae        | 0.0%                          | –                    | –       | –       |
|                 | Meriones libycus         | 1.1%                          | 0.4–2.3%             |         |         |
|                 | Meriones persicus        | 6.5%                          | 3.0–12.4%            |         |         |
|                 | Meriones shawi           | 0.0%                          | –                    | –       | –       |
|                 | Psammomys obesus         | 39.1%                         | 26.0–53.5%           |         |         |
|                 | Psammomys vestiaris      | 27.6%                         | 14.0–45.4%           |         |         |
|                 | Rhombomys opimus         | 0.3%                          | 0.0–1.2%             |         |         |
|                 | Tatera indica            | 0.8%                          | 0.2–2.7%             |         |         |
| Murinae         | Apodemus sylvaticus      | 11.45%                        | 10.11–12.78%         |         |         |
|                 | Lemniscomys barbarus     | 2.2%                          | 1.2–3.5%             | < 0.001 |         |
|                 | Mastomys erythroleucus   | 0.0%                          | –                    | –       | –       |
|                 | Mus musculus             | 16.6%                         | 12.8–20.9%           |         |         |
|                 | Mus spretus              | 19.4%                         | 11.6–29.7%           |         |         |
|                 | Nesokia indica           | 0.0%                          | –                    | –       | –       |
|                 | Rattus norvegicus        | 16.4%                         | 14.0–19.0%           |         |         |
|                 | Rattus rattus            | 9.9%                          | 6.9–13.6%            |         |         |
| Sciurinae       | Sciurus vulgaris         | 20.0%                         | 8.4–39.6%            |         |         |

A P-value ≤ 0.05 is considered statistically significant.

spread by phlebotomine sand flies. Unfortunately, these types of studies are difficult to carry out in wildlife.

The aim of this review is to provide an overview of studies dealing with the potential role of rodents in the life cycle of L. infantum and the current epidemiological status of leishmaniosis in the Mediterranean basin.

MATERIALS AND METHODS

Search and Eligibility Criteria
A bibliographic search was carried out in the databases of Google Scholar, Ovid, Pubmed, ScienceDirect, Scopus, and Web of Science. The general terms “leishmania infantum,” “epidemiology,” and “detection” were used, together with the MeSH term “rodentia.” If the latter was not accepted, it was replaced by the general term “rodent.” The selected articles were those dealing with studies on rodent species as leishmaniosis reservoirs in the Mediterranean area. Other inclusion criteria were the language (English) and date of publication (between January 1, 1995 and December 31, 2020). This review was carried out essentially based on guidelines outlined in the study published in Research Synthesis Methods (22).

Restricting the review to studies published in English may be considered a limitation, as the Mediterranean area has a wide diversity of languages. Nevertheless, as all the studies included here have been published in indexed journals, their rigor is ensured. We have also referenced the four articles found in the search that have an abstract in English but were excluded from the review as otherwise they are written in Turkish (one) (23) and French (one) (24).

Statistics
The SPSS program, version 25.0 (SPSS, Chicago, IL, USA), and the GraphPad Prism Software program, version 8.0 (La Jolla, CA, USA) were used for the different statistical analyses performed. The normality of the different variables studied was verified with the Kolmogorov-Smirnov test (P ≥ 0.200). The differences in medians were compared using the Mann-Whitney U test (for two independent variables) or the Kruskal-Wallis test (for more than two independent variables), because they were non-parametric variables. The frequencies of the different variables studied were compared using the X\textsuperscript{2} test. In all cases, P-values < 0.05 were reported as statistically significant.
### TABLE 4 | Median and rank of infection prevalence in the different tissue samples analyzed, the number of positive samples and the number of analyses in Southern Europe between January 2001 and December 2020.

| Parameter                        | Median | Rank          | P-value |
|----------------------------------|--------|---------------|---------|
| **Prevalence of infection (%)**  |        |               |         |
| Blood                            | 18.09  | 5.52 – 70.00  | 0.854   |
| Bone marrow                      | 18.06  | 8.33 – 44.44  |         |
| Leg hair                         | 33.33  | –             |         |
| Liver                            | 19.68  | 12.00 – 33.33 |         |
| Skin                             | 16.67  | 8.33 – 66.67  |         |
| Spleen                           | 13.75  | 4.17 – 33.33  |         |
| More than one sample             | 18.75  | 0.00 – 100.00 |         |
| **Number of positive samples**   |        |               |         |
| Blood                            | 10     | 1 – 19        | 0.545   |
| Bone marrow                      | 2      | 1 – 8         |         |
| Leg hair                         | 2      | –             |         |
| Liver                            | 3      | 2 – 6         |         |
| Skin                             | 2      | 1 – 12        |         |
| Spleen                           | 3      | 1 – 29        |         |
| More than one sample             | 1      | 0 – 16        |         |
| **Number of analyses**           |        |               |         |
| Blood                            | 18     | 4 – 344       | 0.587   |
| Bone marrow                      | 14     | 4 – 24        |         |
| Leg hair                         | 6      | –             |         |
| Liver                            | 17     | 9 – 35        |         |
| Skin                             | 18     | 4 – 35        |         |
| Spleen                           | 24     | 9 – 102       |         |
| More than one sample             | 18     | 2 – 66        |         |

*P-value ≤ 0.05 is considered as statistically significant.*

### RESULTS AND DISCUSSION

A total of 39 articles were included for review (11, 13, 14, 21, 25–59). The number of rodents examined in all the reported studies was 3,643, 302 of which were infected, implying an infection prevalence of 8.3%, (IC<sub>95%</sub> 7.4–9.2) (Supplementary Data Sheets 1, 2). Infection was detected in different sample types using molecular techniques, and only four studies also included serological methods [Dabaghmanesh et al. (29), Tsakmakidis et al. (59), Othman et al. (27), Alcover et al. (13)].

The selected articles were classified as clinical, epidemiological and review studies, the great majority (75%) being epidemiological (Figure 1A). In the last 25 years, the possible role of rodents in the *L. infantum* cycle has been assessed in nine countries of the Mediterranean basin, with the highest number of studies being carried out in Iran. Seven studies were performed in more than one of these nine countries (11, 14, 25, 41, 44, 45, 52) (Figure 1B). If the Mediterranean basin is divided into three large geographical areas, Southern Europe, North Africa and the Middle East, the latter concentrates the greatest number of studies (Figure 1C).

Tables 1, 2 show the number of animals studied in each country and geographical area, as well as the number of infected specimens and prevalence of infection. Statistically significant differences in the proportion of infected hosts were found only between geographical areas, with the highest rate in Southern Europe, above all in Portugal and Spain (more than 25%). When considering the overall prevalence of infection in rodents, a significant difference (P-value of Chi-Square < 0.001) is again apparent between the Middle East (4.5%), North Africa (15.4%), and Southern Europe (14.9%) (Figure 2). The differences observed between these geographical areas may be due to a variable diversity of *Leishmania* species (25, 32), and that rodents have been reported to host more than one species (26). When drawing conclusions from the data reviewed here, it should therefore be taken into account that an animal may be parasitized by more than one species of *Leishmania* or that identification at species level could be absent.

No statistically significant differences were found for the three variables studied (the number of animals captured, number of infected animals, and the median prevalence of infection for each family/subfamily/species) (Figures 1, 3). However, when analyzing the overall prevalence, statistically significant differences become apparent for each species and subfamily, as shown in Table 3. The highest overall infection rate is found in *Mesocricetus auratus* (44), whereas, 10 of the 25 studied species have 0% infection.
| Species of rodentia | Ref. | Country | Sample (positive animals/total animals) | Detection technique | % of positivity (IC_{95%}) | N total detected |
|---------------------|------|---------|----------------------------------------|--------------------|---------------------------|-----------------|
| *Apodemus sylvaticus* | Navea-Pérez et al. (47) | Spain (Granada) | Bone marrow (2/24) 8.33% (0.00–19.39); Spleen (1/24) 4.17% (0.00–12.16); Skin (2/24) 8.33% (0.00–19.39) | PCR-ELISA | 20.8 (4.56–37.04) | 5 |
| | Risueño et al. (21) | Spain (Murcia) | Liver/Spleen/Skin (3/16) 18.75% (0.00–37.88) | Real-time PCR | 18.8 (0.00–37.94) | 3 |
| | Ortuño et al. (48) | Spain (Murcia) | Liver/Spleen/Skin (1/2) 50.00% (0.00–100.0) | Real-time PCR | 50 (0.00–100.0) | 1 |
| *Mus musculus* | Heihazar et al. (36) | Portugal (Sesimbra) | Skin (9/27) 33.33% (15.55–51.11); Liver/Spleen (8/27) 29.63% (12.41–46.85) | PCR-ELISA | 33.3 (15.52–51.08) | 9 |
| | Navea-Pérez et al. (47) | Spain (Granada) | Bone marrow (1/4) 25.00% (0.00–67.44); Blood (1/4) 25.00% (0.00–67.44); Skin (1/4) 25.00% (0.00–67.44) | PCR-ELISA | 50 (1.00–99.00) | 2 |
| | Tsakmakidis et al. (59) | Greece (Macedonia) | Blood/Liver/Spleen (16/66) 24.24% (13.90–34.58); Liver/Spleen (0/66) 0.00% (0.00–0.00); Blood (13/66) 50.00% (30.78–69.22) | qPCR | 24.2 (13.87–34.53) | 16 |
| | Martin-Sánchez et al. (39) | Spain (Granada) | Bone marrow (8/18) 44.44% (21.49–67.40); Spleen (1/18) 5.56% (0.00–16.14); Skin (12/18) 66.67% (44.89–88.44) | PCR-ELISA, qPCR | 88.9 (74.39–100.00) | 16 |
| *Mus speratus* | Millán (48) | Spain (Barcelona) | Blood/Spleen (1/23) 4.35% (0.00–12.68) | Real-time PCR | 4.3 (0.00–12.59) | 1 |
| | Alcover et al. (13) | Spain (Catalonia) | Liver (6/35) 17.14% (4.66–29.63); Skin (5/35) 14.29% (2.69–25.89); Spleen (10/35) 28.57% (13.60–43.54) | qPCR | 42.9 (26.50–59.30) | 9 |
| *Rattus norvegicus* | Psaroulaki et al. (53) | Cyprus | Blood (19/344) 5.52% (3.11–7.94) | IFAT | 5.5 (3.09–7.91) | 19 |
| | Papadogiannakis et al. (50) | Greece (Athens and Piraeus) | Spleen (1/16) 6.25% (0.00–18.11) | nPCR | 6.3 (0.00–18.21) | 1 |
| | Tsakmakidis et al. (59) | Greece (Macedonia) | Blood (7/10) 70.00% (41.60–98.40); Liver/Spleen (0/18) 0.00% (0.00–0.00); Liver/Spleen (0/18) 0.00% (0.00–0.00) | ELISA | 70 (41.60–98.40) | 7 |
| | Heihazar et al. (36) | Portugal (Sintra) | Liver (3/9) 33.33% (2.53–64.13); Spleen (3/9) 33.33% (2.53–64.13) | Microscopy | 33.3 (2.51–64.09) | 3 |
| | Muñoz-Madrid et al. (60) | Spain (Extremadura) | Hair of legs (2/6) 33.33% (0.00–71.05) | Real-time PCR | 33.3 (0.00–71.01) | 2 |
| | Ortuño et al. (48) | Spain (Murcia - Alicante) | Liver, Spleen, Skin (5/5) 100.00% (100.00–100.00) | Real-time PCR | 100 (100.00–100.00) | 5 |
| | Galán-Puchades et al. (33) | Spain (Barcelona) | Spleen (29/102) 28.43% (19.68–37.19) | qPCR | 28.4 (19.65–37.15) | 29 |

(Continued)
TABLE 5 | Continued

| Species of rodentia | Country | Sample (positive animals/total animals) | Detection technique | % of positivity (IC 95 %) |
|---------------------|---------|----------------------------------------|---------------------|--------------------------|
| Sciurus vulgaris | Spain (Catalonia) | Liver (3/25) | 12.00% (0.00–24.74) | Liver or Spleen (3/25) 25.00% (0.00–49.50) |
|                    |         | Spleen (3/25) | 12.00% (0.00–24.74) | Liver or Spleen (3/25) 25.00% (0.00–49.50) |
|                    |         | Skin (2/12) | 16.67% (0.00–37.75) | Liver or Spleen (3/25) 25.00% (0.00–49.50) |

In studies carried out in Southern Europe published between January 2001 and December 2020 (Tables 4, 5), six rodent species were examined in five countries. No statistically significant differences were found related to the different types of sample analyzed (blood, bone marrow, hair, liver, skin, and spleen).

In the studies covered by this review, only some of the criteria outlined by the WHO for defining a species as a reservoir of Leishmania (61) have been met. The reservoir must be sufficiently abundant and long-lived, and there should be continuous contact between the host and vector. Some species of Phlebotomus are described as opportunistic, feeding on the most accessible animals (31, 62). Therefore, if the density of rodents is high, they may be expected to have an increased risk of exposure to the bite of the vector. However, given the complexity of the interactions between the different actors of the transmission cycle (protozoan–vector–mammal), the link between the vector and animal host is difficult to prove (63, 64).

In a reservoir population, the prevalence of Leishmania infantum should be >20%, which has been found for the following rodent species: Cricetulus migratorius (44), Mesocricetus auratus (43, 44), Mus musculus (31, 36, 47, 59), Mus spretus (13), Psammomys obesus (27), Psammomys oxyphilus (27), and Sciurus vulgaris (13). The house mouse (M. musculus), which is native to southwestern Asia (65), is an invasive rodent with a dramatic impact on biodiversity, and human health and activities (66). Asian rodents of the genus Rattus have been implicated in the emergence and spread of infectious diseases affecting human health (67, 68). In the Mediterranean region, the global prevalence of Leishmania infection in the Norway or brown rat (Rattus norvegicus), and the black or roof rat (Rattus rattus) is below 20% but not negligible (9.9 and 16.4%, respectively) (Table 3). Both species merit special attention due to their readiness to colonize urban environments worldwide (69), and their serious impact on global health. Among several publications reporting cases of Leishmania infection in rodents, a study using molecular analysis in an urban area of Brazil found that 16.7% of R. norvegicus, 10% of M. musculus and up to 25% of Cerradomys subflavus, a species native to Brazil, tested positive for L. infantum (70). These results provide evidence that the control of leishmanioses in urban areas should take into consideration the potential transmission role of rodents, especially those species that live alongside humans.

Another relevant factor is the course of infection, which must be non-pathogenic and long enough to allow parasites to survive a season without transmission. Our review shows that rodents with clinical manifestations of Leishmania infection, such as splenomegaly or hepatomegaly, have not been observed in most studies. Finally, parasites must be accessible in the skin or blood of the host in sufficient quantities to be ingested by a sand fly, which was not demonstrated in the reviewed studies. Table 5 details the rank of the median of infection prevalence in the different tissue samples analyzed, which ranges between 13.75% (spleen) and 33.33% (leg hair). In the case of skin samples, the range of infection prevalence is 8.33–66.67%.

Ref. Alcover et al. (Sciurus vulgaris), Zanet et al. (Psammomys obesus, Mus spretus), Navea-Pérez et al. (Sciurus vulgaris), Latorre et al. (Sciurus vulgaris, Mus spretus), Tsakmakidis et al. (Sciurus vulgaris, Mus spretus).
The complexity of the transmission cycle is increased by the diversity of the rodent hosts, as this may give rise to a dilution effect. This hypothesis holds that for vector-borne parasites, the presence of less competent host species may reduce the prevalence of infection in the main host [71] and the relative contribution of each rodent species to the cumulative reservoir can differ [14]. Therefore, the equilibrium of each stage of this complex system of ecological and epidemiological interactions between different hosts, pathogens and vectors is affected by the density of rodent populations.

In total, the studies included in this review investigated 23 species of rodents. The number of specimens per species varies considerably, ranging from one of Funambulus pennantii to 807 of Apodemus sylvaticus. In the latter, 13 specimens (1.6%) were found to be infected (IC<sub>95%</sub> 0.9–2.8). The species with the highest number of infected specimens was Rattus norvegicus: 80 out of 659 animals (9.9%) (IC<sub>95%</sub> 12.1–14.9). The highest rate of infection was found in Mesocricetus auratus, but only four specimens were analyzed, three testing positive (75%) (IC<sub>95%</sub> of 67.7%). These results indicate that there is still insufficient data available to define which species may have a significant impact on the transmission cycle of the parasite.

**CONCLUSION**

The detection of *Leishmania* infection in rodents, regardless of the species, suggests that these animals may contribute to maintaining the life cycle of *L. infantum*. Further, studies employing xenodiagnosis should shed more light on this role. Additionally, experimental and analytical studies are necessary to evaluate which type of sample and technique are the most suitable to detect the infection. Despite the challenging nature of rodent control, more information about this zoonotic parasite carried by rodent populations in the Mediterranean basin is required to develop suitable surveillance plans and intervention strategies.

**AUTHOR CONTRIBUTIONS**

MA and RF designed the research study and wrote the manuscript. MA, MR, and RF contributed with data analysis and interpretation. All authors read and approved the final version of the manuscript.

**ACKNOWLEDGMENTS**

The authors thank ATP biostatistical consulting for technical support on statistical testing. Grateful acknowledgment to Lucy Brzoska for her advice on the English preparation of the manuscript.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2021.702687/full#supplementary-material
infected *Phlebotomus perniciosus*. *Trans R Soc Trop Med Hyg.* (1985) 79:524–6. doi: 10.1016/0033-9203(85)90085-9

17. Svobodová M, Votýpka J. Experimental transmission of *Leishmania tropica* to hamsters and mice by the bite of *Phlebotomus sergenti*. *Microbes Infect.* (2003) 5:471–4. doi: 10.1016/S1286-4579(03)00066-2

18. Svobodová M, Votýpka J, Nicolás L, Volč P. *Leishmania tropica* in the black rat (*Rattus rattus*): persistence and transmission from asymptomatic host to sand fly vector *Phlebotomus sergenti*. *Microbes Infect.* (2003) 5:361–4. doi: 10.1016/S1286-4579(03)00046-7

19. Grammatica M, Gradoni L. The current status of zoonotic leishmaniasis and approaches to disease control. *Int J Parasitol.* (2005) 35:1169–80. doi: 10.1016/j.ijpara.2005.07.001

20. Hallmäier-Wacker LK, Munster VJ, Knauf S. Disease reservoirs: from conceptual frameworks to applicable criteria. *Emerg Microbes Infect.* (2017) 6:e79. doi: 10.3390/11837615

21. Risueño J, Ortuzo M, Pérez-Cutillas P, Goyena E, Maia C, Cortes S, et al. Epidemiological and genetic studies suggest a common *Leishmania infantum* transmission cycle in wildlife, dogs and humans associated to vector abundance in Southeast Spain. * Vet Parasitol.* (2018) 259:61–67. doi: 10.1016/j.vetpar.2018.05.012

22. Polanin JR, Piggot TD, Espelage DL, Grotpeter JK. Best practice guidelines for *Leishmania tropica*. *Trans R Soc Trop Med Hyg.* (2012) 106:1353–5. doi: 10.1093/trstmh/trs075

23. Özbilgin A, Çavuş I, Yıldırım A, Gündüz C. Do the rodents have a role in transmission of cutaneous Leishmaniasis in *Turkey*? *Microbiol Bull.* (2018) 52:259–72. doi: 10.5578/mh.66682

24. Derbali M, Chelbi I, Ben Hadj Ahmed S, Zhioua E. *Leishmania major*. *Syn Meth* (2019) 10:330–42. doi: 10.1016/j.syme.2019.06.003

25. Aoun K, Bouratbine A. Cutaneous *Leishmania* in North Africa: a review. *Bull Soc Pathol Exot* Scopoli, 1786 (Diptera: Psychodidae).

26. Alcover et al. Molecular detection of *Leishmania infantum* infection in rodent reservoirs in Jahron District, Southern Iran. *Sotoodeh-Jahromi A, et al. Molecular survey on detection of Trans R Soc Trop Med Hyg.* (2019) 66:961–73. doi: 10.1093/apt/jptb.2014.10419

27. Mirzaei A, Schweynoch C, Rouhani S, Parviz P, Schonian G. Diversity of *Leishmania infantum* and *L. major* in Algeria. *Trans R Soc Trop Med Hyg.* (2018) 125:69–73. doi: 10.1093/trstmh/trx085

28. Mirzaei A, Schwynoch C, Rouhani S, Parviz P, Schönian G. Diversity of *Leishmania* species and of strains of *Leishmania major* isolated from desert rodents in different foci of cutaneous leishmaniasis in Iran. *Trans R Soc Trop Med Hyg.* (2014) 108:502–12. doi: 10.1093/trstmh/tru083

29. Moradi M, Rassi Y, Abai MR, Zahraei Ramazani A, Mohobeli M, Rafizadeh S. Some epidemiological aspects of cutaneous leishmaniasis with emphasis on vectors and reservoirs of disease in the borderline of Iran and Iraq. *J Parasit Dis*. (2018) 42:243–51. doi: 10.1016/s0146-6053(17)30166-6

30. Mostafa BH, Souha BA, Sabkh F, Noureddine Ch, Riadh BS. Evidence for the existence of two distinct species: *Phomomomys obesus* and *Psammomys* within the sand rats (Rodentia, Gerbillinae), reservoirs of cutaneous leishmaniasis. *Infect Genet Evol.* (2006) 6:301–8. doi: 10.1016/j.ijge.2005.09.002

31. Navea-Pérez HM, Diaz-Sáez V, Corpas-López V, Merillas-Márquez F, Diaz-Sáez V. Vertical transmission may play a greater role in the spread of *Leishmania infantum* in synanthropic *Mus musculus* rodents than previously believed. *Transbound Emerg Dis.* (2020) 67:1113–18. doi: 10.1111/tbed.13436

32. Ortuño M, Latrofa MS, Iborra MA, Pérez-Cutillas P, Bernal LJ, Risueño J. Genetic diversity and phylogenetic relationships between *Leishmania* species isolated from rodent reservoirs in southern Iran, *2012. Asian Pac J Trop Biom*. (2014) 4:5575–80. doi: 10.12980/AJPTB.4.2014.10419

33. Millán J. Molecular investigation ofvector-borne parasites in wild micromammals, Barcelona (Spain). *Parasitol Res.* (2018) 117:3015–18. doi: 10.1007/s00436-018-5971-y

34. Hajjaran H, Mohebali M, Teimouri A, Oshaghi MA, Mirjalali H, Kazemi-A, Khaze V, et al. Molecular epidemiology of cutaneous leishmaniasis and heterogeneity of *Leishmania major* strains in Iran. *Trop Med Int Health.* (2017) 12:1335–44. doi: 10.1111/tmi.12954

35. Harrat Z, Pratlong F, Belazouz S, Dereeje J, Deniau M, Rioux JA, et al. *Leishmania infantum* and *L. major* in Algeria. *Trans R Soc Trop Med Hyg.* (1996) 90:625–9. doi: 10.1016/0033-9309(96)90410-1

36. Hajjaran H, Mohebali M, Teimouri A, Oshaghi MA, Mirjalali H, Kazemi-Rad E, et al. Identification and phylogenetic relationship of Iranian strains of various *Leishmania* species isolated from cutaneous and visceral cases of leishmaniasis based on N-acetylglucosamine-1-phosphate transferase gene. *Infect Genet Evol.* (2014) 26:203–12. doi: 10.1016/j.meegid.2014.05.026
Leishmania infantum in Rodents in the Mediterranean Basin

52. Pratlong F, Dereure J, Ravel C, Lami P, Ballard Y, Serres G, et al. Geographical distribution and epidemiological features of Old World cutaneous leishmaniasis foci, based on the isoenzyme analysis of 1048 strains. *Trop Med Int Health.* (2009) 14:1071–85. doi: 10.1111/j.1365-3156.2009.02336.x

53. Psaroulaki A, Antoniou M, Tzoumazos P, Matzeris A, Ioannou I, Chochlakis D, et al. Rats as indicators of the presence and dispersal of six zoonotic microbials in Cyprus, an island ecosystem: a seroepidemiological study. *Trans R Soc Trop Med Hyg.* (2010) 104:733–9. doi: 10.1016/j.trstmh.2010.08.005

54. Quinnell RJ, Courtenay O. Transmission, reservoir hosts and control of zoonotic visceral leishmaniasis. *Parasitology.* (2009) 136:1915–34. doi: 10.1017/S0031182009991156

55. Rassi Y, Gassemi MM, Javidian E, Rafizadeh S, Motazedian H, Vatandoost H. Vectors and reservoirs of cutaneous leishmaniasis in Marvdasht district, southern Islamic Republic of Iran. *East Mediterr Health J.* (2007) 13:686–93.

56. Sofizadeh A, Hanafi-Bojd AA, Shoraka HR. Modeling spatial distribution of *Rhombomys opimus* as the main reservoir host of zoonotic cutaneous leishmaniasis in northeastern Iran. *J Vector Borne Dis.* (2018) 55:297–304. doi: 10.4103/0972-9062.256565

57. Souguir-Omrani H, Chemkhi J, Fathallah-Mili A, Saadi-BenAoun Y, BelHadjAli Y, Guizani I, et al. *Paraechinus aethiopicus* (Ehrenberg 1832) and *Atelerix algirus* (Lereboullet 1842) hedgehogs: possible reservoirs of endemic leishmaniasis in Tunisia. * Infect Genet Evol.* (2018) 63:219–30. doi: 10.1016/j.meegid.2018.05.029

58. Tomassone I, Bertrattu E, De Sousa R, Duscher GG, Mihalca AD, Silaghi C, et al. Neglected vector-borne zoonoses in Europe: into the wild. * Vet Parasitol.* (2018) 251:17–26. doi: 10.1016/j.vetpar.2017.12.018

59. Tsakmakidis I, Angelopoulou K, Dovas CI, Dokianakis E, Tamvakis A, Symeonidou I, et al. Leishmania infection in rodents in Greece. *Trop Med Int Health.* (2017) 22:1523–32. doi: 10.1111/tmi.12982

60. Muñoz-Madrid R, Belinchón-Lorenzo S, Iniesta V, Fernández-Cotrina J, Parejo JC, Serrano FJ, et al. First detection of Leishmania infantum kinetoplast DNA in hair of wild mammals: Application of qPCR method to determine potential parasite reservoirs. *Acta Tropica.* (2013) 128:706–9. doi: 10.1016/j.actatropica.2013.08.009

61. World Health Organization. *Control of the leishmaniasis.* WHO Technical Report Series no. 949. Geneva: The Organization (2010).

62. de Colmeneres M, Portàs M, Botet J, Dobaño C, Gállego M, Wolff M, et al. Identification of blood meals of *Phlebotomus pernicosus* (Diptera: psychodidae) in Spain by competitive enzyme-linked immunoadsorbent assay biotin/avidin method. *J Med Entomol.* (1995) 32:229–33. doi: 10.1093/jmedent/32.3.229

63. Glass GE, Cheek JE, Patz JA, Shields TM, Doyle TJ, thoroughman DA, et al. Using remotely sensed data to identify areas at risk for hantavirus pulmonary syndrome. *Emerg Infect Dis.* (2006) 6:238–47. doi: 10.3201/eid0603.060303

64. Ostfeld RS, Holt RD. Are predators good for your health? Evaluating evidence for top-down regulation of zoonotic disease reservoirs. *Front Ecol Environ.* (2004) 2:13–20. doi: 10.1890/1540-9295(2004)002[0013:APGFYH]2.0.CO;2

65. Suzuki H, Nunome M, Kinoshita G, Aplin KP, Vogel P, Kryukov AP, et al. Evolutionary and dispersal history of Eurasian house mice *Mus musculus* clarified by more extensive geographic sampling of mitochondrial DNA. * Heredity (Edinb).* (2013) 111:375–90. doi: 10.1038/hdy.2013.60

66. Singleton GR, Hinds LA, Krebs CJ, Spratt DM. *Rats, Mice and People: Rodent Biology and Management.* Canberra, ACT: ACIAR Monograph 96 Australian Centre for International Agricultural Research (2003).

67. Morand S, Bordes F, Hsuan-Wien C, Julien C, Cosson JF, Maxime G, et al. Global parasite and *Rattus* rodent invasions: the consequences for rodent-borne diseases. *Integr. Zool.* (2015) 10:409–23. doi: 10.1111/1749-4877.12143

68. Wells K, O’Hara RB, Morand S, Lessard JP, Ribas A. The importance of parasite geography and spillover effects for global patterns of host-parasite associations in two invasive species. *Divers Distrib.* (2015) 21:477–86. doi: 10.1111/ddi.12297

69. Aplin KP, Suzuki H, Chinen AA, Chesser RT, Have JT, Donnellan CS, et al. Multiple geographic origins of commensalism and complex dispersal history of Black Rats. *Plos ONE.* (2011) 6:e26357. doi: 10.1371/journal.pone.0026357

70. de Castro Ferreira E, Cruz I, Cañavate C, de Melo I A, Sampaio Pereira A A, Madeira F A M, et al. Mixed infection of Leishmania infantum and *Leishmania braziliensis* in rodents from endemic urban area of the New World. *Vet Res.* (2015) 11:71. doi: 10.1186/s12917-015-0392-y

71. Telfer S, Bown K, Jekseles R, Begon M, Hayder I, Birtles R. Disruption of a host-parasite system following the introduction of an exotic host species. *Parasitology.* (2005) 132( Pt. 6):661–8. doi: 10.1017/S0031182005007250

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a shared affiliation with the authors MA, MR, and RF at time of review.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Alcover, Riera and Fisa. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.