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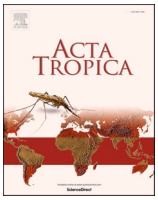

A global perspective on non-autochthonous canine and feline *Leishmania* infection and leishmaniosis in the 21st century

Rafael Rocha [a], André Pereira [b,c], Carla Maia [a,*]

[a] Global Health and Tropical Medicine (GHTM), Instituto de Higiene e Medicina Tropical (IHMT), Universidade NOVA de Lisboa, Lisboa 1349-008, Portugal
[b] Faculdade de Medicina Veterinária, Universidade Lusófona, Lisboa 1749-024, Portugal
[c] Escola Superior de Saúde, Proteção e Bem Estar Animal, Instituto Politécnico da Lusofonia, Lisboa 1749-024, Portugal

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ABSTRACT

Leishmaniosis is a high-burden vector-borne disease caused by *Leishmania* parasites that affect humans and other animals, including dogs and cats. Globalization is one of the main factors that largely contributes to the spread of leishmaniosis to non-endemic areas. A comprehensive review of scientific literature published between 2000 and 2021 was conducted to identify the epidemiological situation and clinical management of imported animal *Leishmania* infection and leishmaniosis as a fundamental step to better manage individual cases and traveler animal health from a global and One Health perspective. A total of 31 articles were selected, representing 1403 canine, and 25 feline imported cases. Canine and feline leishmanioses in non-endemic areas remain a challenge for veterinarians. Thus, diagnostic and management algorithms for veterinary clinical decision support are proposed. Increased surveillance of non-autochthonous cases, including relocated companion animals, could improve individual health, and mitigate the public and animal health risk of introducing *Leishmania* species into new areas.

1. Introduction

Leishmaniosis is a negligible parasitic disease caused by kinetoplastid protozoa of the genus *Leishmania* which is transmitted to vertebrates via infected female phlebotomine sand flies. The disease is prevalent in tropical and subtropical regions and can be geographically separated into Old World (OW) and New World (NW) leishmaniosis, with distinct species occurring in different regions (Akhoundi et al., 2017). At least 20 *Leishmania* species are recognized as pathogenic to humans, most of them of zoonotic origin. Although clinical manifestations of human leishmaniosis are largely diverse, two primary clinical forms are frequently reported worldwide: visceral leishmaniosis (VL) and cutaneous leishmaniosis (CL). The first is typically caused by parasites of the *L. donovani* complex (i.e., *L. donovani* in the OW and *L. infantum* in both the OW and NW) and can be fatal if untreated (World Health Organization WHO, 2022).

Contrary to *L. donovani*, the life cycle of *L. infantum* is mostly zoonotic, with dogs universally recognized as the primary domestic reservoir hosts for human infection. Nevertheless, cats have also a non-neglected role in the epidemiology of zoonotic visceral leishmaniosis and are currently considered the most probable additional domestic reservoir hosts of *L. infantum* (Maia et al., 2018).

Currently, integrated, and complete data regarding *Leishmania* infection and leishmaniosis in both dogs and cats are not available in most endemic countries (Berriatua et al., 2021) and reporting of canine and feline leishmanioses in non-endemic areas is also not a current practice. Like humans, the movement of domestic animals poses a risk to the health of animals traveling to endemic areas, just as the importation of infected companion animals to non-endemic areas poses a risk to animal and public health (Maia and Cardoso, 2015; Wright et al., 2020).

Therefore, this study aimed to summarize and analyze the epidemiology, clinical presentation, diagnosis, and management of non-autochthonous *Leishmania* infection and leishmaniosis in companion animals (i.e., dogs and cats), through a comprehensive review of the literature in the last 22 years (2000–2021) to raise awareness of the veterinary community regarding the challenges associated with the diagnosis and management of this parasitosis.

2. Search strategy, eligibility, and review

A comprehensive literature search was performed on 12 November 2021 by sourcing National Library of Medicine (NLM) resources through

* Corresponding author.
E-mail address: carlamaia@ihmt.unl.pt (C. Maia).

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PubMed (https://pubmed.ncbi.nlm.nih.gov/) using the following Boolean string: ("leish*"[All Fields] AND ("travel"[MeSH Terms] OR "travel"[All Fields] OR "trip"[All Fields] OR "trips"[All Fields] OR "traveling"[All Fields] OR "travelling"[All Fields] OR "travels"[All Fields] OR "traveled"[All Fields] OR "traveler"[All Fields] OR "traveler s"[All Fields] OR "travelers"[All Fields] OR "travelled"[All Fields] OR "traveller"[All Fields] OR "traveller s"[All Fields] OR "travellers"[All Fields] OR ("migrate"[All Fields] OR "migrated"[All Fields] OR "migrates"[All Fields] OR "migrating"[All Fields] OR "migration"[All Fields] OR "migrational"[All Fields] OR "migrant"[All Fields] OR "migrants"[All Fields] OR "migrations"[All Fields] OR "migrator"[All Fields] OR "migrators"[*All Fields*]) OR ("import"[All Fields] OR "importation"[All Fields] OR "importations"[All Fields] OR "imported"[All Fields] OR "importer"[All Fields] OR "importers"[All Fields] OR "importing"[All Fields] OR "imports"[*All Fields*])) AND ("dogs"[MeSH Terms] OR "dogs"[All Fields] OR "dog"[All Fields] OR ("canine s"[All Fields] OR "dogs"[MeSH Terms] OR "dogs"[All Fields] OR "canine"[All Fields] OR "canines"[*All Fields*]) OR "cat"[All Fields] OR ("cats"[MeSH Terms] OR "cats"[All Fields] OR "felines"[All Fields] OR "felidae"[MeSH Terms] OR "felidae"[All Fields] OR "feline"[*All Fields*]).

Search results were saved as a comma-separated value (CSV) file, and subsequently imported into Microsoft Excel®. Study eligibility was manually assessed by two independent researchers in a blinded manner. All records were screened according to the title, and abstract, if available. Only studies published between 2000 and 2021 were included, even if the cases reported were diagnosed in previous years. Only original research articles reporting dogs or cats with non-autochthonous *Leishmania* infection (i.e., reportedly infected by *Leishmania* parasites in a country different than the one they were living in at the moment of diagnosis) were retained, including those published in some languages other than English (Fig. 1).

The presence of repeated cases in different articles was assessed – either confirmed, when explicitly mentioned in the text; or suspected, based on the authors, place of infection, year, and place of diagnosis (including hospital or center). Articles, where all or most cases reported, had (certainly or likely) been previously described in the literature were mostly discarded (except if they contained clinical or epidemiological details not published in previous works). Articles, where some cases in a series had (certainly or likely) been previously described, were retained, but some cases were discarded - either entirely or in part of the information. This verification process of repeated cases was performed manually and for all the selected articles.

Some records had missing data, and the denominators mentioned in the text and tables count only those where data was available. Articles, where the place of infection included a list of several countries, were counted for the region of infection, but not for the country of infection. The same principle was applied to the place of diagnosis. Regions of infection/diagnosis were defined based on the World Bank Group proposed regions. Activity (travel or importation of animals) was classified based on original articles' information.

Only laboratory-confirmed cases of *Leishmania* infection were included in this review, including both clinical leishmaniosis and subclinical infection. Methods and samples for diagnosis were included only when specified for each animal in the article. Besides counting the number of individuals in which each test was performed, the result of the test for each animal was registered: positive (suggestive or confirmatory of *Leishmania* infection) or negative. Species/complex identification was only considered when the articles mentioned laboratory confirmation, even though the exact technique may not be specified. Even though some articles mention identification to the species level, for result analysis and discussion purposes, cases caused by species of the *L. donovani* complex (i.e., *L. donovani* and *L. infantum*) are presented together, following the classification proposed by Maurício (2018):

- *Leishmania* (*Leishmania*) subgenus: *L donovani* complex [*L. donovani, L. infantum* (syn. *L. chagasi*)].

Clinical signs and laboratory findings were extracted, whenever available, using the terms contained in the original articles. Animals with splenomegaly, hepatomegaly or both were grouped under the same category. Animals with unspecific clinical signs were also grouped. Information regarding co-infections with parasitic and bacterial pathogens was also included.

3. Results and discussion

3.1. Canine Leishmania infection and leishmaniosis

A total of 28 articles were selected, according to selection criteria, representing a total of 1403 cases of non-autochthonous leishmaniosis or subclinical infection in dogs (Best et al., 2014; Cleare et al., 2014; Dandrieux et al., 2018; Farkas et al., 2011; Gin et al., 2021; Hamel et al., 2012, 2011; Helm et al., 2013; Iqbal et al., 2002; Kawamura et al., 2010; Kotnik et al., 2021; Latif et al., 2019; Leschnik et al., 2008; Menn et al.,

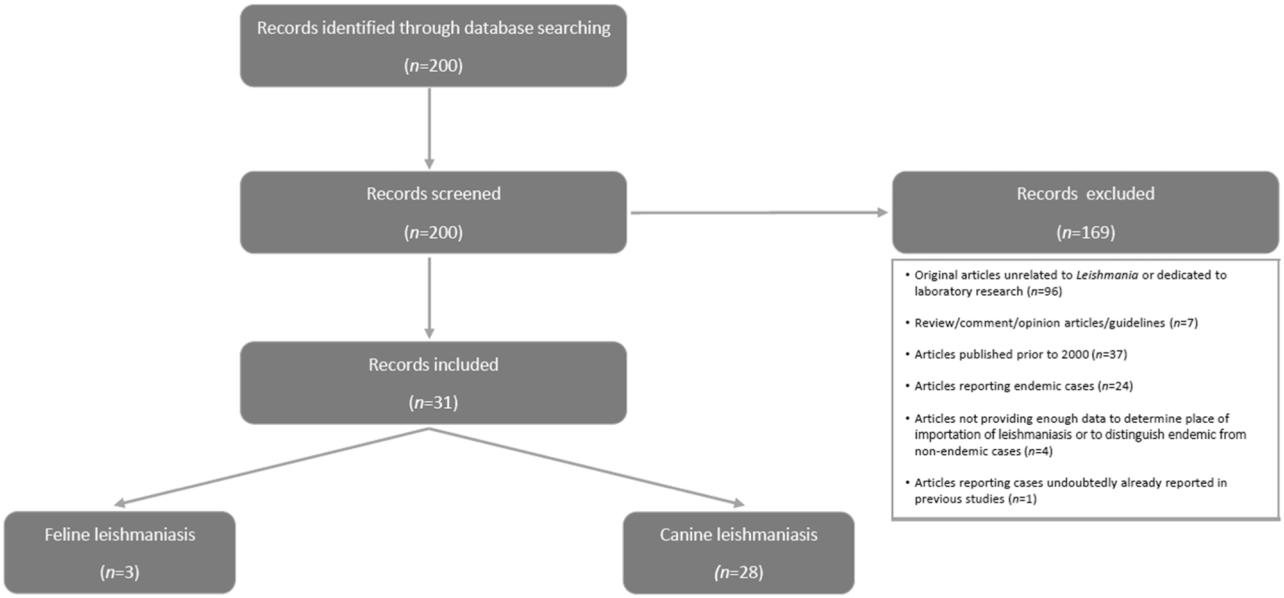

Fig. 1. Flow diagram of study search and selection process.

2010; Naucke et al., 2016; Pavel et al., 2017; Rotureau et al., 2006; Schäfer et al., 2019a, 2019b; Shaw et al., 2008; Schönian et al., 2003; Silvestrini et al., 2016; Tanase et al., 2018; Teske et al., 2002; Vilhena et al., 2014; Wagner et al., 2020; Willi et al., 2015). For 689 individuals, the likely place of infection was described, comprising 22 different countries or territories, represented in Fig. 2. In 673 of the 689 (97.7%) cases, infection with *Leishmania* parasites was assumed to have occurred in Europe (Table 1) and most of the animals (1331/1403) were diagnosed in this continent, including 56% in Germany (Hamel et al., 2012, 2011; Menn et al., 2010; Naucke et al., 2016; Schäfer et al., 2019a, 2019b; Schönian et al., 2003), 25% in the UK (Dandrieux et al., 2018; Shaw et al., 2008; Shaw et al., 2003; Silvestrini et al., 2016) and 12% in the Netherlands (Teske et al., 2002). Cases represented either importation of infected animals (317/461) or infection during travel (144/461), especially to *L. infantum* endemic areas (144/461) (Table 1). Indeed, travel data shows that the largest percentage of people traveling to Southern Europe are Europeans, including from non-endemic areas (Stark et al., 2008), so it could be assumed that most traveller dogs are also from this region. In terms of place of likely infection, it is not surprising that almost all cases reported infection in the Mediterranean region since this has been largely recognized as the main focus of *Leishmania* infection in dogs, with seroprevalence exceeding 50% in some studies in this region (Gálvez et al., 2020). Countries identified outside the European region where cases were diagnosed included Angola ($n = 1$, (Vilhena et al., 2014)), Australia ($n = 6$, (Best et al., 2014; Cleare et al., 2014)), Canada ($n = 1$, (Wagner et al., 2020)), Japan ($n = 2$, (Kawamura et al., 2010)) and South Africa ($n = 2$, (Latif et al., 2019)); all of them were dogs imported from Europe, except for one from Angola (Latif et al., 2019) and one from Morocco (Wagner et al., 2020). Venereal and vertical transmission routes have also been described in the literature (Naucke and Lorentz, 2012) and this review identified one case where transmission in a non-endemic setting was attributed to venereal transmission (Rotureau et al., 2006).

Although not retrieved in our search, additional cases in the literature suggest autochthonous chains of transmission of canine leishmaniosis in non-endemic settings started by an imported index case. In some of these cases, transplacental transmission to one or more generations seems likely (Svobodova et al., 2017), whereas in others transmission via bite wounds (McKenna et al., 2019; Naucke et al., 2016) and/or semen (Karkamo et al., 2014) was suspected. Therefore, clinical suspicion of leishmaniosis in non-endemic areas should not be restricted to dogs imported from endemic regions, but also considered in their offspring and in dogs sharing the same household.

The presence or absence of clinical signs was mentioned for 807 dogs, with 790 presenting clinical disease. In sick dogs, the most frequently described signs were skin lesions (64.1%) (Best et al., 2014; Dandrieux et al., 2018; Farkas et al., 2011; Helm et al., 2013; Kawamura et al., 2010; Latif et al., 2019; Pavel et al., 2017; Rotureau et al., 2006; Tanase et al., 2018; Wagner et al., 2020), lymphadenopathy (38.5%) (Best et al., 2014; Cleare et al., 2014; Dandrieux et al., 2018; Pavel et al., 2017; Silvestrini et al., 2016; Tanase et al., 2018; Vilhena et al., 2014) and general/miscellaneous signs (41.0%) (Dandrieux et al., 2018; Helm et al., 2013; Naucke et al., 2016; Silvestrini et al., 2016; Tanase et al., 2018; Willi et al., 2015), such as anorexia, weight loss and lethargy (Table 2). Common laboratory findings included: anemia (61.2%) (Cleare et al., 2014; Dandrieux et al., 2018; Farkas et al., 2011; Helm et al., 2013; Pavel et al., 2017; Silvestrini et al., 2016; Tanase et al., 2018; Willi et al., 2015), hypoalbuminemia (58.8%) (Best et al., 2014; Cleare et al., 2014; Dandrieux et al., 2018; Helm et al., 2013; Naucke et al., 2016; Silvestrini et al., 2016), hypergammaglobulinemia (41.3%) (Cleare et al., 2014; Dandrieux et al., 2018; Silvestrini et al., 2016), azotemia (23.8%) (Dandrieux et al., 2018; Naucke et al., 2016; Silvestrini et al., 2016), leukopenia (23.8%) (Cleare et al., 2014; Helm et al., 2013; Silvestrini et al., 2016; Tanase et al., 2018), and thrombocytopenia (20.0%) (Cleare et al., 2014; Dandrieux et al., 2018; Silvestrini et al., 2016; Tanase et al., 2018; Willi et al., 2015). Coinfection with other vector-borne pathogens was identified in 47 animals, with *Babesia* spp. ($n = 17$) (Ganjaei et al., 2018; Hamel et al., 2012, 2011; Schäfer et al., 2019b; Shaw et al., 2003) and *Ehrlichia* spp. ($n = 16$) (Hamel et al., 2011; Leschnik et al., 2008; Schäfer et al., 2019a, 2019b) being the most often identified (Table 2).

Despite the importance of subclinical infection in dogs in the maintenance of endemic cycles (Campino and Maia, 2018), targeted research in this field in imported/traveler animals has been very scarce. Only four epidemiological studies clearly mentioned screening of healthy dogs for diagnosis of subclinical infection (Cleare et al., 2014; Hamel et al., 2012;

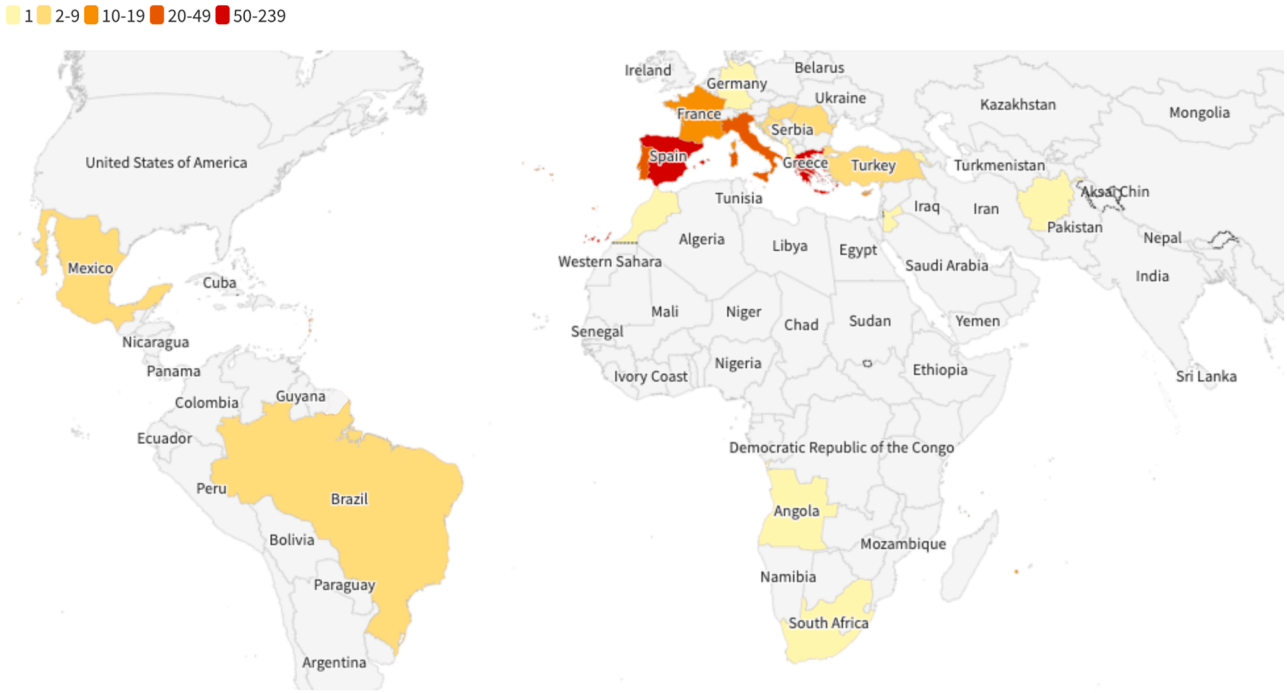

Fig. 2. Number of cases of *Leishmania* infection and leishmaniosis diagnosed in dogs, by country of importation or travel.

Table 1
Epidemiological aspects of non-autochthonous canine *Leishmania* infection and leishmaniosis cases.

Description	Frequency	Refs.
Sex		
Male	58.8% (10/17)	Cleare et al. (2014), Dandrieux et al. (2018), Kawamura et al. (2010), Latif et al. (2019), Pavel et al. (2017), Rotureau et al. (2006), Willi et al. (2015)
Female	41.2% (7/17)	Best et al. (2014), Cleare et al. (2014), Kawamura et al. (2010), Latif et al. (2019), Naucke et al. (2016), Tanase et al. (2018), Vilhena et al. (2014)
Median age (range)	6 yr (3–12 yr)	(Best et al. (2014), Cleare et al. (2014), Dandrieux et al. (2018), Kawamura et al. (2010), Latif et al. (2019), Naucke et al. (2016), Pavel et al. (2017), Tanase et al. (2018), Vilhena et al. (2014), Willi et al. (2015)
Region of infection		
Europe	97.7% (673/689)	(Best et al. (2014), Cleare et al. (2014), Dandrieux et al. (2018), Farkas et al. (2011), Gin et al. (2021), Hamel et al. (2012 (2011), Helm et al. (2013), Kawamura et al. (2010), Kotnik et al. (2021), Latif et al. (2019), Mettler et al. (2005), Naucke et al. (2016), Pavel et al. (2017), Rotureau et al. (2006), Schäfer et al. (2019a (2019b), Schönian et al. (2003), Shaw et al. (2008), Shaw et al. (2003), Silvestrini et al. (2016), Tanase et al. (2018), Teske et al. (2002), Vilhena et al. (2014), Wagner et al. (2020), Willi et al. (2015)
Latin America and Caribbean	0.9% (6/689)	Gin et al. (2021), Helm et al. (2013), Silvestrini et al. (2016)
Central Asia	0.7% (5/689)	Gin et al. (2021)
Sub-Saharan Africa	0.3% (2/689)	Latif et al. (2019), S.E. Shaw et al. (2003)
Middle East	0.1% (1/689)	Gin et al. (2021)
North Africa	0.1% (1/689)	Wagner et al. (2020)
South Asia and East Asia	0.1% (1/689)	Gin et al. (2021)
Region of diagnosis		
Europe	94.8% (1331/1403)	Dandrieux et al. (2018), Farkas et al. (2011), Hamel et al. (2012, 2011), Helm et al. (2013), Kotnik et al. (2021), Leschnik et al. (2008), Menn et al. (2010), Mettler et al. (2005), Naucke et al. (2016), Pavel et al. (2017), Schäfer et al. (2019a, 2019b), Schönian et al. (2003), Shaw et al. (2008), Shaw et al. (2003), Silvestrini et al. (2016), Tanase et al. (2018), Teske et al. (2002), Vilhena et al. (2014), Willi et al. (2015)
America	4.4% (62/1403)	Gin et al. (2021), Rotureau et al. (2006), Wagner et al. (2020)
	0.6% (8/1403)	
Asia and Oceania		Best et al. (2014), Cleare et al. (2014), Zanger et al. (2011)
Africa	0.2% (3/1403)	Latif et al. (2019), Vilhena et al. (2014)
Activity		
Imported	68.8% (317/461)	Best et al. (2014), Cleare et al. (2014), Gin et al. (2021), Hamel et al. (2012), Helm et al. (2013), Latif et al. (2019), Mettler et al. (2005), Naucke et al. (2016), Pavel et al. (2017), Rotureau et al. (2006), Schäfer et al. (2019b), Shaw et al. (2003), Silvestrini et al. (2016), Tanase et al. (2018), Teske et al. (2002), Vilhena et al. (2014), Wagner et al. (2020), Willi et al. (2015)
Traveler	31.2% (144/461)	Dandrieux et al. (2018), Farkas et al. (2011), Hamel et al. (2011), Helm et al. (2013), Kawamura et al. (2010), Kotnik et al. (2021), Mettler et al. (2005), Schäfer et al. (2019a), Silvestrini et al. (2016), Teske et al. (2002)
Stage of disease		
Clinical	56.3% (790/1403)	Best et al. (2014), Cleare et al. (2014), Dandrieux et al. (2018), Farkas et al. (2011), Gin et al. (2021), Helm et al. (2013), Kawamura et al. (2010), Kotnik et al. (2021), Latif et al. (2019), Leschnik et al. (2008), Mettler et al. (2005), Naucke et al. (2016), Pavel et al. (2017), Rotureau et al. (2006), Schäfer et al. (2019a, 2019b), Schönian et al. (2003), Shaw et al. (2008), Shaw et al. (2003), Silvestrini et al. (2016), Tanase et al. (2018), Teske et al. (2002), Vilhena et al. (2014), Wagner et al. (2020), Willi et al. (2015)
Not described	42.5% (596/1403)	Hamel et al. (2011), Menn et al. (2010)
Subclinical	1.2% (17/1403)	Cleare et al. (2014), Hamel et al. (2012), Kotnik et al. (2021)

Kotnik et al., 2021; Shaw et al., 2003). The absence of routine screening of imported healthy animals could facilitate the circulation of *Leishmania* in non-endemic regions and countries, which could represent a potential risk for the introduction of the parasite in places where permissive vectors are present, as recently observed in Northern Italy (Gradoni et al., 2022). Laboratory diagnosis of *Leishmania* infection was described in 1087 cases (Table 3). Positivity rates using parasitological techniques were high for both polymerase chain reaction (PCR; 96.1%) and microscopy (i.e., cytology and/or histology; 92.9%). Lymph node biopsy or aspirate was the biological samples more often used for cytology/histology, and blood for PCR. Serological testing was used in over 90% of dogs, especially the immunofluorescence antibody test IFAT (72.3%). Positivity rates exceeded 90% with all the serological techniques, with the lowest reported with ELISA (93.8%). Species identification was performed in 71 cases and parasites belonging to the *L. donovani* complex were identified as the causative species in all (Best et al., 2014; Cleare et al., 2014; Dandrieux et al., 2018; Gin et al., 2021;

Table 2
Coinfections and treatment of non-autochthonous canine *Leishmania* infection and leishmaniosis.

Description	Frequency	Refs.
Clinical signs		
Skin lesions	64.1% (50/78)	Best et al. (2014), Dandrieux et al. (2018), Farkas et al. (2011), Helm et al. (2013), Kawamura et al. (2010), Latif et al. (2019), Pavel et al. (2017), Rotureau et al. (2006), Tanase et al. (2018), Wagner et al. (2020)
Constitutional signs	41.0% (32/78)	Dandrieux et al. (2018), Helm et al. (2013), Naucke et al. (2016), Silvestrini et al. (2016), Tanase et al. (2018), Willi et al. (2015)
Lymphadenopathy	38,5% (30/78)	Best et al. (2014), Cleare et al. (2014), Dandrieux et al. (2018), Pavel et al. (2017), Silvestrini et al. (2016), Tanase et al. (2018), Vilhena et al. (2014)
Gastrointestinal signs	5.1% (4/78)	Cleare et al. (2014), Naucke et al. (2016), Vilhena et al. (2014), Willi et al. (2015)
Ocular lesions	5.1% (4/78)	Farkas et al. (2011), Pavel et al. (2017), Wagner et al. (2020), Willi et al. (2015)
Edema	2.6% (2/78)	Nadler et al. (2014), Pavel et al. (2017)
Fever	2.6% (2/78)	Pavel et al. (2017), Willi et al. (2015)
Genitourinary signs	2.6% (2/78)	Kawamura et al. (2010), Pavel et al. (2017)
Hepatosplenomegaly	2.6% (2/78)	Best et al. (2014), Tanase et al. (2018)
Skin/mucosal hemorrhage	2.6% (2/78)	Best et al. (2014), Pavel et al. (2017)
Respiratory signs	1.3% (1/78)	Willi et al. (2015)
Coinfections		
Babesia spp.	36.2% (17/47)	Ganjaei et al. (2018), Hamel et al. (2012, 2011), Schäfer et al. (2019b), Shaw et al. (2003)
Ehrlichia spp.	34.0% (16/47)	Hamel et al. (2011), Leschnik et al. (2008), Schäfer et al. (2019a, 2019b)
Rickettsia spp.	17.0% (8/47)	Leschnik et al. (2008)
Dirofilaria spp.	8.5% (4/47)	Leschnik et al. (2008), Schäfer et al. (2019b)
Multiple	4.3% (2/47)[a]	Schäfer et al. (2019b)
Treatment strategy		
Systemic	83.4% (156/187)	
Allopurinol alone	67.3% (105/156)	Cleare et al. (2014), Helm et al. (2013), Silvestrini et al. (2016), Willi et al. (2015)
Allopurinol + second drug	32.1% (50/156)[b]	Best et al. (2014), Cleare et al. (2014), Kawamura et al. (2010), Silvestrini et al. (2016), Tanase et al. (2018), Wagner et al. (2020)
Pentamidine	0.6% (1/156)	Rotureau et al. (2006)
None	16.6% (31/187)	Mettler et al. (2005)
Relapses	0.5% (1/187)	Wagner et al. (2020)

[a] *Babesia* sp. + *Dirofilaria immitis* ($n = 1$); *Babesia* sp. + *D. immitis* + *Ehrlichia canis* ($n = 1$).
[b] Second drug: meglumine antimoniate ($n = 31$); miltefosine ($n = 16$); ketoconazole ($n = 2$); liposomal amphotericin B ($n = 1$).

Table 3
Diagnostic approach of canine non-autochthonous *Leishmania* infection and leishmaniosis.

Description	Frequency tested	Frequency tested positive, *n* (%)	Refs.
Serology	95.4% (1037/1087)	98.8% (1000/1012)	
IFAT	72.2% (698/967)	99.7% (696/698)	Best et al. (2014), Cleare et al. (2014), Farkas et al. (2011), Hamel et al. (2012 (2011), Menn et al. (2010), Schäfer et al. (2019a, 2019b)
ELISA	16.5% (160/967)	93.8% (150/160)	Cleare et al. (2014), Dandrieux et al. (2018), Kotnik et al. (2021), Mettler et al. (2005), Naucke et al. (2016), Schäfer et al. (2019a, 2019b), Tanase et al. (2018)
DAT	15.1% (146/967)	100% (146/146)	Teske et al. (2002), Vilhena et al. (2014)
rK39	0.3% (3/967)	100% (3/3)	Kawamura et al. (2010)
PCR	12.6% (137/1087)	96.1% (74/77)	
Blood	58.5% (38/65)	92.1% (35/38)	Best et al. (2014), Cleare et al. (2014), Dandrieux et al. (2018), Hamel et al. (2012), S. E. Shaw et al. (2003), Wagner et al. (2020), Willi et al. (2015)
Lymph node	13.8% (9/65)	100% (9/9)	Best et al. (2014), Pavel et al. (2017)
Bone marrow	12.3% (8/65)	100% (8/8)	Best et al. (2014), Cleare et al. (2014)
Spleen	12.3% (8/65)	100% (8/8)	
Skin	10.8% (7/65)	100% (7/7)	Best et al. (2014), Cleare et al. (2014), Kawamura et al. (2010)
Others	10.8% (7/65)[c]	100% (7/7)	Helm et al. (2013), Silvestrini et al. (2016), Willi et al. (2015)
Microscopy[a]	2.2% (24/1087)	92.9% (26/28)	
Lymph node	54.2% (13/24)	84.6% (11/13)	Cleare et al. (2014), Naucke et al. (2016), Pavel et al. (2017)
Spleen	20.8% (5/24)	100% (5/5)	Best et al. (2014), Cleare et al. (2014)
Bone marrow	16.7% (4/24)	100% (4/4)	Best et al. (2014), Cleare et al. (2014)
Skin[b]	12.5% (3/24)	100% (3/3)	Cleare et al. (2014), Kawamura et al. (2010), Latif et al. (2019)
Other	12.5% (3/24)	100% (3/3)	Cleare et al. (2014)
Culture	0.3% (3/1087)	75.0% (3/4)	
Skin	66.7% (2/3)	50.0% (1/2)	Kawamura et al. (2010), Wagner et al. (2020)
Bone marrow	33.3% (1/3)	100% (1/1)	Cleare et al. (2014)
Blood	33.3% (1/3)	100% (1/1)	Cleare et al. (2014)

[a] Cytology and/or histology.
[b] Biopsy, scrapping or smear.
[c] Synovial fluid ($n = 5$); conjunctival smear ($n = 1$).
Abbreviations: PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; IFAT, immunofluorescence antibody test; DAT, direct agglutination test; rK39, rapid immunochromatographic test.

Kawamura et al., 2010; Pavel et al., 2017; Schönian et al., 2003; Vilhena et al., 2014; Wagner et al., 2020; Willi et al., 2015).

Management strategy was described for 187 sick animals (Table 2). In spite of early treatment being considered fundamental in interrupting a potential introduction of the parasite in new areas where vector species are present (Vulpiani et al., 2011), thirty-one of the infected dogs (16.6%) were not treated; for those treated, allopurinol was used as a monotherapy in 67.3% of cases and in combination with a second drug in 32.1% of animals, most often meglumine antimoniate (62%) or miltefosine (32%); other combination drugs included ketoconazole and liposomal amphotericin B (LAmB). As the results reinforce the growing need for professional veterinary awareness of *Leishmania* infection in non-endemic countries (Maia and Cardoso, 2015; Wright et al., 2020), Fig. 3 provides a proposal of a diagnosis, management, and prevention algorithm for canine *Leishmania* infection and leishmaniosis in non-endemic settings.

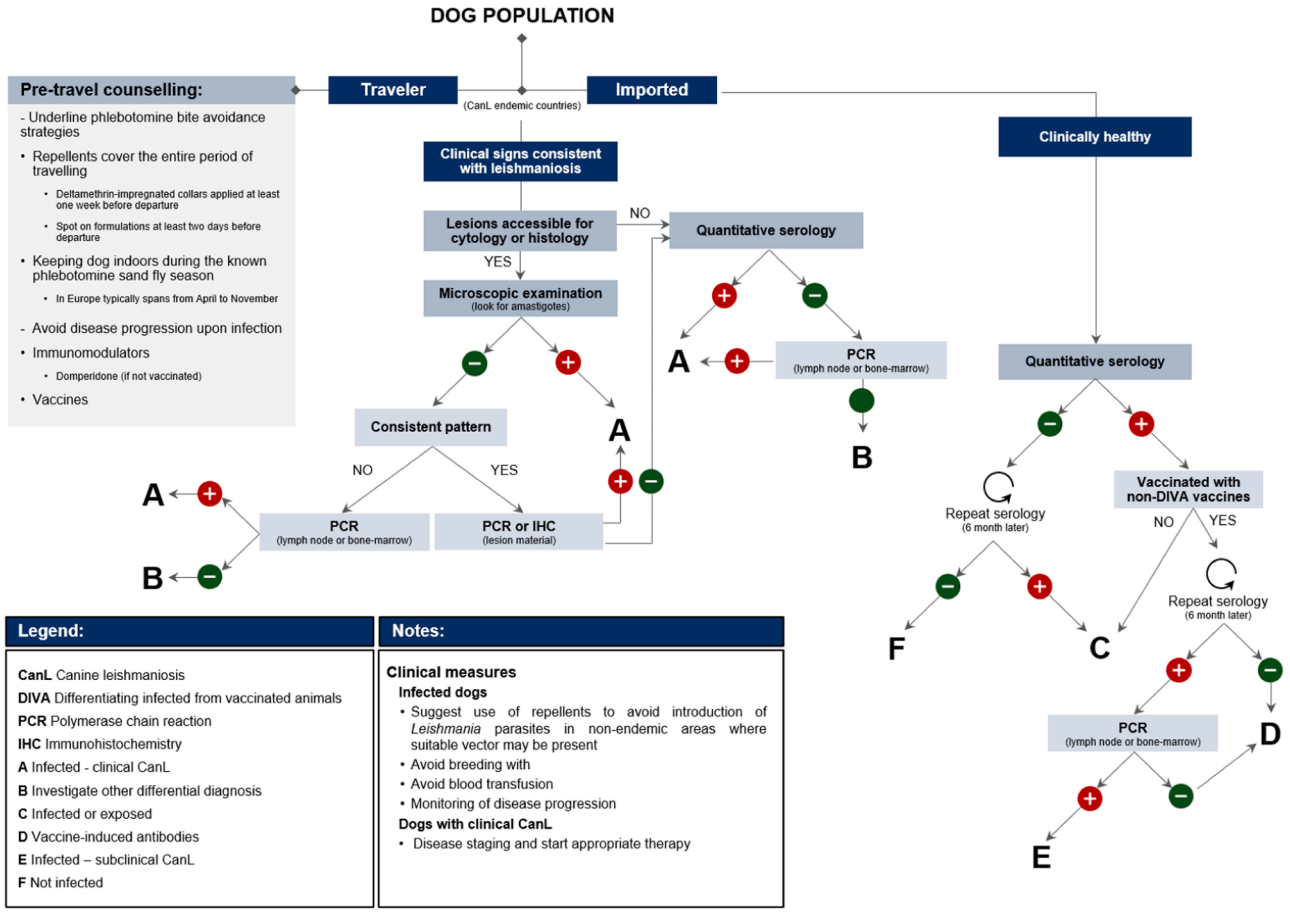

Fig. 3. Proposed algorithm to approach and management of canine *Leishmania* infection and leishmaniosis in non-endemic settings.

3.2. Feline leishmaniosis

According to selection criteria, a total of 25 cases of non-autochthonous feline leishmaniosis were identified and diagnosed either in Germany ($n = 22$, (Schäfer et al., 2021)) or in Switzerland ($n = 3$, (Richter et al., 2014; Rüfenacht et al., 2005)). For 11 of these cats, likely region of infection was assumed to have been Europe, namely Spain ($n = 8$, (Richter et al., 2014; Rüfenacht et al., 2005; Schäfer et al., 2021)), Greece ($n = 2$, (Schäfer et al., 2021)) and Romania ($n = 1$, (Schäfer et al., 2021)). Four cats were infected outside Europe and, for the remaining, no information was available about the region of infection. Quantitative serology was used and positive in all 25 cases: ELISA ($n = 2$, (Rüfenacht et al., 2005)) and IFAT ($n = 23$, (Richter et al., 2014; Schäfer et al., 2021)). Species of the *Leishmania donovani* complex were identified as the causative agent in 13 cases. Coinfection was reported in 12 cats: *Hepatozoon* spp. ($n = 3$), *Rickettsia* spp. ($n = 3$), *Dirofilaria* spp. ($n = 1$), *Ehrlichia* spp. ($n = 2$), *Ehrlichia* spp. and *Rickettsia* spp. ($n = 2$), *Hepatozoon* spp. and *Rickettsia* spp. ($n = 1$). Three case reports provided information on clinical presentation, diagnosis, and treatment strategy: the three cats presented skin lesions and hyperglobulinemia (Richter et al., 2014; Rüfenacht et al., 2005) and one had ocular signs (Richter et al., 2014). *Leishmania* DNA was detected by PCR in biological samples of the three cats, namely skin (Rüfenacht et al., 2005) and bone marrow and spleen (Richter et al., 2014), while the presence of amastigotes was visualized by cytology in the bone marrow and lymph node aspirates of one cat (Rüfenacht et al., 2005) and in a corneal smear of another (Richter et al., 2014). The three cats were successfully treated with allopurinol monotherapy (Richter et al., 2014) as no failures or relapses were described.

The presence of *Leishmania* infection in cats has been increasingly reported in endemic areas (Pereira and Maia, 2021), and current evidence suggests that cats play a role as reservoir hosts of *L. infantum* (Maia and Campino, 2011). Thus, from an animal and public health point of view, veterinarians should include leishmaniosis in the differential diagnosis of cats with skin lesions, ocular signs, cytopenia and hyperglobulinemia, especially after travel/importation from endemic areas. In addition, occasional or systematic screening for asymptomatic infection in imported/traveling cats may provide more information about the risk of imported leishmaniosis to the local feline population. Fig. 4 provides an algorithm for the diagnostic and management of feline *Leishmania* infection and leishmaniosis in non-endemic settings.

4. Conclusion

Almost 1500 cases of non-autochthonous *Leishmania* infection were reported between 2000 and 2021, in dogs and, to a lesser extent, in cats, reflecting the impact of this parasitosis on global tourism and movement of animals. Improved clinical management (by veterinarians) and surveillance of non-autochthonous cases could improve individual health and mitigate the animal and public health risk of introducing *Leishmania* into new areas where favorable environmental conditions and permissive vectors exist. Strengthening surveillance and systematically combining animal and human data into an integrated platform, following a One Health approach, could be the key to addressing the risk of leishmaniosis introduction associated with increased human and animal mobility.

CRediT authorship contribution statement

Rafael Rocha: Methodology, Validation, Formal analysis,

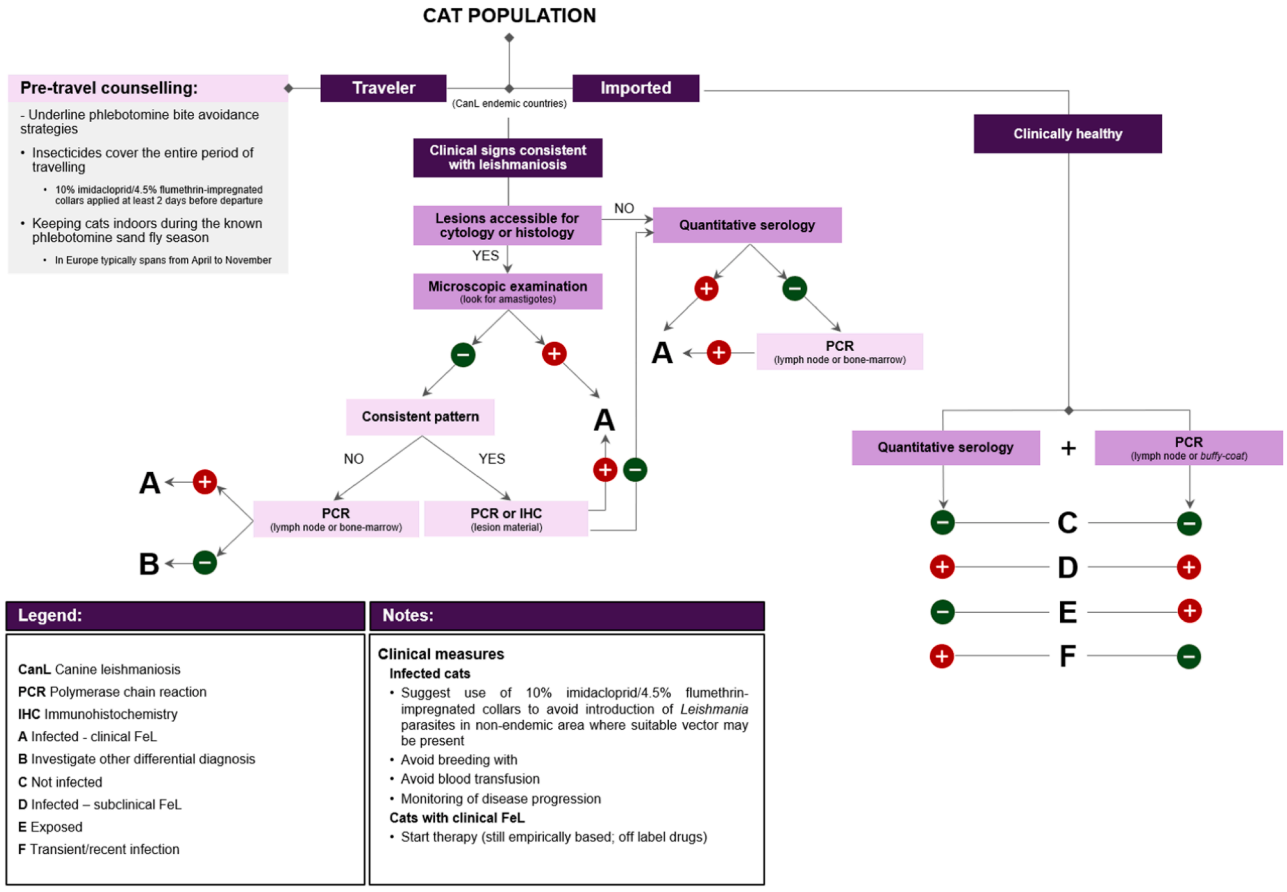

Fig. 4. Proposed algorithm to approach and management of feline *Leishmania* infection and leishmaniosis in non-endemic settings.

Investigation, Writing – original draft. **André Pereira:** Validation, Formal analysis, Writing – original draft. **Carla Maia:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

No data was used for the research described in the article.

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