Journal of Comparative Pathology 209 (2024) 6–12

Contents lists available at ScienceDirect

Journal of Comparative Pathology

journal homepage: www.elsevier.com/locate/jcpa

Infectious disease: Review article

Sand fly-borne diseases in Europe: epidemiological overview and potential triggers for their emergence and re-emergence

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ARTICLE INFO

Article history:
Received 10 November 2023
Accepted 3 January 2024

Keywords:
climate change
emergence
environmental changes
epidemiology
Europe
human-made changes
Leishmania
One Health
Phlebovirus
sand fly-borne diseases

ABSTRACT

Phlebotomine sand flies (Diptera: Phlebotominae) are vectors of human and animal pathogens, including *Leishmania* species protozoan parasites and viruses of the genus *Phlebovirus*. In Europe, visceral zoonotic leishmaniasis caused by *Leishmania infantum*, a deadly disease when left untreated, is endemic in southern countries, and dogs are the main reservoir hosts for human infection. Most phleboviruses cause asymptomatic infections or flu-like syndromes in humans, but Toscana phlebovirus can cause meningitis and encephalitis. These diseases are likely to re-emerge, posing a growing threat to public and animal health. Potential triggers include the movement of humans and dogs, increasing numbers of immunosuppressive conditions, climate change and other human-mediated environmental changes. An overview of the main epidemiological characteristics of the pathogens transmitted by sand flies in Europe and the potential triggers involved in their emergence and re-emergence are reviewed here. There is a need to implement mandatory notification of human and canine leishmaniases and human phleboviruses and coordinated epidemiological surveillance programmes at a European level, and to raise awareness among healthcare professionals and citizens about sand fly-borne diseases, following a One Health approach.

Contents

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https://doi.org/10.1016/j.jcpa.2024.01.001

1. Introduction

Phlebotomine sand flies (Diptera: Phlebotomine) are present in tropical/subtropical areas and temperate zones of the world including southern Europe, Asia, Africa, Australia and the Americas. About 1,000 species have been estimated to exist and a conservative approach to group them in genera recognizes *Phlebotomus*, *Sergentomyia*, *Chinius*, *Idiophlebotomus* and *Australophlebotomus* in the Old World and *Lutzomyia*, *Brumptomyia*, *Hertigia* and *Warileya* in the New World, with *Phlebotomus* and *Lutzomyia* being the main genera with medical importance [1–3].

Sand flies are strictly terrestrial in all stages of their development (egg, four larva instars, pupa and adult) and only females require a blood meal to develop their eggs. The seasonal activity of adults is affected mainly by temperature and rainfall, which in temperate regions, such as Europe, triggers species to overwinter as diapausing 4th instar larvae [1].

The importance of sand flies in Public and Animal Health is that they are the vectors of *Leishmania* parasites, the causative agents of leishmaniases [4]. These insects are also involved in the transmission of several viral agents (genera *Phlebovirus* and *Vesiculovirus* in the Old World and New World, and *Orbivirus* in the New World) of biomedical importance [5], and are the vectors of the bacterium *Bartonella bacilliformis*, which causes Carrion's disease in a limited Andean region [6].

Over 21 species of *Leishmania* are recognized as pathogenic for humans [7–9]. Clinical manifestations of leishmaniases are diverse, although two main clinical forms are prevalent worldwide: (1) visceral leishmaniasis (VL), also known as kala-azar, affecting macrophage-rich tissues such as spleen, liver and bone marrow, and which is fatal in most cases if left untreated; and (2) cutaneous leishmaniasis (CL), the most common form of the disease characterized by skin lesions on exposed parts of the body; this form is benign but often leaves life-long disfiguring scars [4]. More than 98 countries and territories in four continents have reported endemic transmission of leishmaniasis. According to the World Health Organization (WHO), about one billion people are at risk of contracting the infection, and 50,000–90,000 new cases of VL and up to one million of CL occur annually [10].

Sand fly-borne viruses have a worldwide geographic distribution. Most human infections appear to be subclinical, but when symptomatic their clinical spectrum varies from a self-limited febrile illness ('3-day fever', 'Pappataci fever' or 'sand fly fever') or formation of vesicles on the oral mucosa, lips and nose (vesicular stomatitis), to involvement of the peripheral and central nervous systems (summer meningitis and Chandipura virus encephalitis) [5]. The worldwide incidence of viruses transmitted by sand flies is unknown, but it is estimated that in the Mediterranean area at least 250 million people are exposed to phlebovirus infections [11].

Transmission of different pathogens by the sand fly to the vertebrate host is biological. Transmission of *Leishmania* parasites occurs when an infected female, during a new blood meal, inoculates the infective metacyclic promastigotes into the vertebrate host [12].

Viruses, in addition to horizontal transmission, can be transmitted venereally and transovarially by feeding on an infected sugar source or by co-feeding [13–19].

According to their ability to support late-stage development of different *Leishmania* species under experimental conditions, sand flies have been classified into three categories: (1) specific or restrictive vectors, when they display strict specificity for *Leishmania* species, as is the case of *Phlebotomus papatasi* and *Paraphlebotomus sergenti*, which, respectively, support late-stage development of *Leishmania major* (the aetiological agent of zoonotic CL in the Old World) and *Leishmania tropica* (the aetiological agent of anthroponotic [ie, transmissible from humans to humans] CL in the Old World); (2) permissive vectors, when they support late-stage development of multiple *Leishmania* species, as is the case of most *Phlebotomus* and *Lutzomyia* species, and can act as potential vectors of several parasite species, thus facilitating the establishment of new foci of leishmaniasis; and (3) refractory species, which do not support the development of *Leishmania* parasites [12]. On the other hand, sand fly species seem to be permissive to the development of different viruses [20,21].

2. Sand fly-borne pathogens in Europe: an epidemiological overview

Zoonotic VL and CL caused by *Leishmania infantum* are endemic in southern European countries and dogs are the main and reservoir hosts for human infection [22]. Parasites are transmitted by several *Phlebotomus* species mainly belonging to the subgenus *Larroussius* (eg, *Phlebotomus ariasi*, *Phlebotomus perniciosus*, *Phlebotomus tobbi*) [12]. *L. infantum* is considered the only autochthonous (ie, locally acquired) species in Europe in the first decade of the 21st century, except for sporadic cases of local transmission of anthroponotic CL caused by *L. tropica* and of VL and CL caused by *Leishmania donovani* (the aetiologic agent of anthroponotic VL and of post-kala-azar dermal leishmaniasis, a sequela of VL, in East Africa and the Indian subcontinent) in Greece [23] and Cyprus [24], respectively. The estimated number of VL and CL cases in the WHO European Region is 1,100–1,900 and 10,000–17,000 cases per 100,000 population, respectively [25].

The presence of *L. infantum* parasites in dogs can range from a chronic infection without clinical signs, lasting several years, to a very serious illness that can quickly progress to death [26]. In fact, subclinical infections are much more frequent than clinical disease, with canine seroprevalence of *Leishmania* in southern European countries being estimated to be between 5% and 30% [27].

Humans are accidental hosts of *L. infantum* and the risk of infection depends on the number of infected animal reservoir hosts and vectors living close to humans. Until the second half of the 20th century VL was mainly a paediatric disease (with the most affected age group being 0–5 years); this declined in numbers mostly due to socioeconomic changes favouring better nutrition and housing [28]. In the early 1990s, the disease gained attention due to the impact of co-infections with *L. infantum* and human immunodeficiency virus (HIV), with most cases reported in adults from southwestern countries [29]. By the end of the 1990s, the *L. infantum*/HIV epidemic peak had declined due to the introduction of highly active antiretroviral therapy, and currently most VL cases occur in adults, with an increasing number in immunosuppressed patients due to co-morbidities or therapies [22].

Zoonotic VL is a rural disease in areas and villages with vegetation, where many people have dogs and other domestic animals close to the main habitation attracting sand flies and permitting their breeding and resting. Transmission takes place microfocally due to the opportunistic behaviour of *Phlebotomus* (*Larroussius*) species [30]. However, in recent years the urbanization of leishmaniasis associated with an increasing number of peri-urban residential settlements, providing natural habitats for sand flies, and the increased number of dogs in urban areas, including stray dogs, representing an easy source of blood for sand flies, has facilitated the establishment of *Leishmania* in peripheral areas in southern European countries [28].

Notification of VL is mandatory in endemic countries, except for France and Serbia, and underreporting is considered low because due to its clinical severity, cases are treated in hospital [28,31]. CL is not notifiable in all endemic countries (eg, France, Portugal, Serbia) and in countries in which it is notifiable, it is highly underreported because due to the benignity and self-resolution of the lesions, most patients are frequently treated at primary health centres and private clinics [28,31,32]. Notification of canine leishmaniasis (CanL) is also mandatory in most endemic countries, apart from France, Romania and Serbia, but in some countries this obligation is only applicable to specific regions (eg, Spain) or restricted to cases diagnosed by municipal veterinarians (eg, Portugal) [28,31]. Furthermore, reporting of leishmaniasis in wild animals is also mandatory in some countries. Nonetheless, all countries must report human leishmaniasis cases to the WHO and animal leishmaniasis cases to the World Organisation for Animal Health (WOAH) [28].

Between 2005 and 2020, 17 endemic European countries reported a total of 8,367 human leishmaniasis cases to the WHO: 5,813 were VL cases, of which 94% were autochthonous, and 2,554 were CL cases, of which 53% were imported [22]. In this period, the overall cumulative incidence of VL per 100,000 inhabitants ranged from 2.15 in Albania to 0.002 in Ukraine. The highest cumulative incidence of CL was 0.95 in Malta and it was not reported in Montenegro, North Macedonia and Serbia. In addition to the fact that the number of years in which VL and CL cases were reported to the WHO varied substantially, there was a large discrepancy between these numbers and those obtained through hospital discharges available for some of the endemic countries; according to hospital discharges, the estimated incidence of human leishmaniasis was 0.70 in Italy and the incidences of VL were 0.67 in Spain and 0.41 in Portugal, compared with incidences of 0.16, 0.45 and 0.09 obtained with cases reported to the WHO [22].

Between 2005 and 2020, eight endemic countries reported 4,203 cases of animal leishmaniasis to the WOAH: 4,183 cases in dogs and 20 in wild animals, which was substantially lower than the number of countries that reported autochthonous *L. infantum* infections in dogs and/or other animals in scientific studies published between 2009 and 2020 [22,28].

These data emphasize that hospital discharge databases provide the most accurate information on VL and that underreporting of CL and CanL remains high, reinforcing the need to improve notification systems at the European level [22,28]. Furthermore, there is no evidence that the spatial and temporal distribution of leishmaniasis in Europe has dramatically changed in recent years, although veterinary and public health authorities in some countries consider it an emerging disease, whether at national or regional level [22,31].

Sand fly-borne viruses present in Europe are grouped into the *Phlebovirus* genus with populations living in, or travelling to, southern Europe facing a higher lifetime risk of infection [11,33]. Most human infections with circulating phleboviruses are asymptomatic or show influenza-like syndromes, but Toscana phlebovirus is of public health concern, as outbreaks and sporadic cases of acute meningitis or meningoencephalitis have been reported during the warm season in endemic regions of the Mediterranean Basin [5,11]. None of the phleboviruses transmitted by sand flies are notifiable. In epidemiological surveys carried out in Europe, neutralizing antibodies against Toscana phlebovirus were detected in up to 52% (271/479) of human residents of Cyprus [5] and in up to 8.4% (31/369) of the Cypriot canine population [36], while the prevalences of the Sicilian phlebovirus was up to 32% (155/479) in a normal human population in Cyprus [5] and 71.9% (852/1185) in Greek dogs [36], demonstrating the high level of exposure of vertebrate hosts to these viruses [34–43].

3. Sand fly-borne pathogens in Europe: triggers to their emergence and re-emergence

Transmission of sand fly-borne pathogens is dynamic and their epidemiological complexity in Europe is likely to increase, posing a growing threat to human and animal health. Potential triggers include an increasing number of immunosuppressive conditions, the geographic spread of vectors, climate change, human-mediated environmental changes, identification of potential new reservoir hosts and vector species and the risk of introducing and spreading infections by non-endemic *Leishmania* species associated with increased movement of people and animals through tourism and migration.

3.1. Increasing number of susceptible populations

Following the global trend, the number of populations susceptible to infections due to immunosuppressive factors, comorbidities and ageing is likely to increase in Europe. Furthermore, asymptomatic *L. infantum* infections are common in humans, with an infection prevalence of up to 47% in carriers in southern Europe [44,45]. Therefore, the risk of re-emergence of leishmaniasis associated with increased clinical susceptibility to primary infections or reactivation of latent infections should not be neglected [30,46]. In fact, the number of VL cases in the elderly, probably associated with the impact of immunosenescence, is increasing the risk for other diseases. Likewise in adults medically immunosuppressed by chemical or biological drugs used for organ transplantation, autoimmune diseases or cancer or presenting with immunodeficiencies who live in or travel to endemic countries [28,47].

3.2. Climate change

Leishmaniases are considered climate sensitive diseases, and changes in mean annual temperature and humidity may have direct effects on the ecology of sand flies by altering their geographic distribution and influencing their survival, generation time and population sizes [30].

In Europe, sand fly species are mostly confined to the Mediterranean countries, but the increase in global average temperature has resulted in the geographic expansion of competent vector species to more northern latitudes and to higher altitudes [48–55]. The presence of vectors in new locations and at higher latitude ranges has changed the distribution of *L. infantum* infection, leading to the emergence of new disease foci in endemic countries, as shown through investigations involving canine serosurveys and sand fly monitoring in the north of Italy [56] and in northeast Spain [57,58]. In addition, *L. infantum* local transmission appears to be no longer limited to endemic countries, as autochthonous human and canine cases have been reported in countries considered non-endemic, such as Germany [51] and Romania [59].

The ability of a virus to be transmitted by different sand fly species may facilitate its expansion to new regions where the vectors exist [60], as recently suggested by the detection of supposedly autochthonous meningoencephalitis cases caused by Toscana phlebovirus in southwest Germany [61].

Climate change can also alter the prevalence of leishmaniasis in endemic regions by influencing the bioecology and vectorial capacity of sand flies [30,46]. Temperature changes may have a direct effect on the developmental cycle of the parasite (ie, extrinsic incubation period) in sand flies; experimental evidence suggests that exposure of vectors to a broad range of temperatures compatible with sand fly survival does not inhibit the development of metacyclic promastigotes (ie, the infective parasite stage to the vertebrate host) [62]. Environmental variations may also have indirect impacts on the distribution and seasonal dynamics of vector species; in Mediterranean areas where the mean annual temperature remains higher for longer, the period of activity of proven vectors of *L. infantum* was longer and their density and number of generations were found to be higher [63].

3.3. Human-made environmental changes

Environmental changes induced by humans can also influence the epidemiology of leishmaniasis, as observed in Fuenlabrada, a city near Madrid, in Spain, where 446 cases of human leishmaniasis (160 VL and 286 CL) were diagnosed between 2009 and 2012, mainly in immunocompetent adults lacking acquired immunity to the parasite [64]. The area had long been known to be endemic for *L. infantum*, with sporadic human cases and a low prevalence in dogs. This outbreak, the largest to have occurred in Europe, was related to the construction of a peri-urban green park enclosed by roads, houses and other infrastructure. The construction of the park allowed hares, and to a lesser extent rabbits, to multiply in the absence of predators and to become a major blood source for the local competent vector *P. perniciosus*, leading to the establishment of a new sylvatic/peri-domestic transmission cycle, with lagomorphs as the main reservoir hosts for *L. infantum* parasites [65,66].

3.4. Identification of potential new reservoir hosts

A *Leishmania* reservoir host must be susceptible to the parasite and infection should be long-lasting to increase the chance of parasites being transmitted to the vector; it should live in close contact with humans and vectors and should be a good source of parasites to the vectors [4]. As previously mentioned, domestic dogs are the main reservoir hosts of *L. infantum*; however, a role for wild and other domestic animals in the epidemiology of this *Leishmania* species has been suggested [67]. Among these, special attention should be given to synanthropic species present in high numbers and for which measures to control or avoid contact with sand fly vectors are limited or absent, namely domestic cats and urban rats.

The increasing tendency of domestic cats to be considered potential reservoir hosts of the parasite is based on: (1) their susceptibility to infection and, in some cases, to the development of clinical disease, which was demonstrated by the high prevalence of exposed cats infected with the parasite; (2) because they are a frequent source of blood for vectors, as revealed by the analysis of the blood sources of sand flies, and by demonstration, through detection of antibodies against the saliva of *P. perniciosus*, that in endemic areas cats are bitten frequently by sand flies; (3) their ability to present parasites in an available form (ie, in blood and skin) to be transmitted to vectors (ie, infected cats are infectious for sand fly vectors as proven by xenodiagnoses) [68].

The involvement of rodents in the zoonotic transmission of *L. infantum* in urban environments is suggested by the high prevalence of infection found in populations of Norway rats (*Rattus norvegicus*) and *P. perniciosus* present in the underground sewers of Barcelona (Spain) [69]. Thus, sewage systems in cities appear to offer ideal breeding and resting places for rats and sand flies, allowing intense contact between them, which facilitates the circulation of *L. infantum* parasites and increases the risk of their transmission to other vertebrate hosts that are close to sewers.

3.5. Identification of potential new sand fly vectors

The rigorous incrimination of a sand fly species as a vector is based on five criteria [4,70], but due to the difficulty of complying with some of them, as they depend on the establishment of laboratory sand fly colonies, the inclusion of a species as a proven or suspected vector has three minimum requirements [2]: (1) it must feed on humans; (2) it must support natural infections with parasites of the same *Leishmania* species that infect humans; and (3) it must have a strong ecological association, including seasonality, with humans, indicated by the overlap of their geographic distribution and human disease.

As previously mentioned, in Europe L. *infantum* parasites are transmitted by *Phlebotomus* species belonging mainly to the subgenus *Larroussius*; however, there is evidence that other sand fly species belonging to other genera [71] and subgenera, namely *Sergentomyia minuta* and *Phlebotomus* (*Transphlebotomus*) *mascittii*, may be involved in its circulation.

Sand flies of the genus *Sergentomyia* are widely distributed in the Old World, being present at high densities in many of the endemic foci of leishmaniasis [3]. Originally, they were assumed to feed only on reptiles and therefore considered to transmit only *Leishmania* parasites of the subgenus *Sauroleishmania*. However, it has been shown that *S. minuta* (a species present in the Mediterranean basin) feeds on mammals, and *Leishmania* species pathogenic to humans and animals (namely *L. infantum* and *L. major*) have been detected by molecular testing in specimens captured in southern Europe [72–75].

P. mascittii is the northernmost and most widely distributed sand fly species in Europe [12,76]. Although this species is generally regarded as cavernicolous, it was recently recorded in microhabitats near domestic animals and human dwellings. Its involvement in the transmission of *L. infantum* is suggested because the parasite's DNA has been detected in specimens collected in Austria and Italy and some supposedly autochthonous cases of leishmaniasis in humans and animals have been described in regions where it was the only species of sand fly present.

Therefore, there is increasing evidence of the involvement of these two sand fly species (*S. minuta* and *P. mascittii*) in the circulation of mammalian parasites. This, combined with the growth in the number of *Leishmania* reservoir hosts due to travel and importation of dogs in areas considered non-endemic [77] but where these two species of sand flies are present, reinforces the importance of investigating their vectorial competence with regard to: (1) their capacity to support the development of metacyclic promastigotes after the digestion of an infectious blood meal; and (2) their ability to transmit the parasite through biting to a susceptible host [71].

3.6. Identification of novel phleboviruses

The genetic diversity within the *Phlebovirus* genus is greater than initially anticipated [5], as demonstrated by the increasing number of novel viruses detected in the last decade in Europe. This is exemplified by the detection in sand flies of Fermo phlebovirus in Italy [78] and of Alcube virus and Arrabida virus in Portugal [79,80], and reports of fever syndromes caused by Cyprus virus [81] and Adria virus [82]. The emergence of new species and variants, associated with the propensity of segmented RNA viruses for genetic reassortment or recombination, may pose a risk to public and animal health [83].

3.7. Risk of introduction of exotic Leishmania species

In addition to the current distribution of leishmaniases in Europe, consideration should be given to the risk of introduction of non-endemic *Leishmania* species. The risk depends on contact between infected hosts and sand flies, the potential role as reservoir hosts played by infected humans or animals and the vector competence of European sand flies for the dispersal of introduced *Leishmania* strains/species [2,46,84,85].

This scenario is very likely due to the combined effects of globalization associated with tourism and the movement of migrants, as exemplified by the diagnosis of imported VL and CL caused by various *Leishmania* species of the Old World and New

World in 15 European laboratory centres [86] and by the comprehensive review of imported human leishmaniasis cases diagnosed globally between 2000 and 2021 [47]. The risk of introduction seems to be higher for *Leishmania* species of anthroponotic transmission, such as *L. tropica* and *L. donovani*.

In the case of *L. tropica*, the wide geographic distribution of its proven vector, *P. sergenti*, in southern Europe may give rise to new endemic foci through the introduction of infected humans to areas where this sand fly species is present. It should be noted that the development of *L. tropica*, under experimental conditions, in other sand fly species present in Europe, namely in *P. perniciosus* and in *P. tobbi*, and the ability of the former to transmit viable parasites to a vertebrate host, has recently been demonstrated by xenodiagnosis assays, supporting the hypothesis that in certain epidemiological situations, *Larroussius* species may play the role of occasional *L. tropica* vectors [87,88].

Establishment of the *L. donovani* cycle in Europe through the introduction of infected humans is also a possibility, due to the wide geographic distribution of *Phlebotomus* (*Larroussius*) species permissive to the parasite [12,89]. Available information shows an increase in the number of imported VL cases caused by *L. donovani* in endemic and non-endemic European countries associated with increased human travelling and migration [47]. However, differentiating species from the *L. donovani* complex (composed of *L. infantum* and *L. donovani sensu stricto* [s.s.]) based on genetic analysis is a challenge and may lead to unnoticed spread of *L. donovani s.s*. Into new areas, as recently suggested to have occurred in Turkey [90].

Although the risk of establishment of *L. major* in Europe is considered low, as its gerbillid reservoir hosts are not present on the continent, this assumption has recently been challenged, as voles of the genus *Microtus* have been implicated as *L. major* reservoir hosts in a CL focus in northern Israel [91]. As such, there is the possibility that *L. major*, having adapted to voles, could spread north into Turkey and southern Europe, where these putative reservoir hosts and their proven vector, *P. papatasi* exist in sympatry. In fact, *L. major* DNA was recently identified in the spleen of an *Apodemus* species in a Turkish province [92], reinforcing the view that the geographic spread of this *Leishmania* species is a probability, given that species of murid rodents of the genus *Apodemus*, which are widespread throughout southern European countries (eg, the European wood mouse [*Apodemus sylvaticus*]), could facilitate its dissemination. Interestingly, the presence of *L. major* has already been reported in Portugal through detection of its DNA in a sand fly female of the species *S. minuta* [73] and in a young stray cat [93], suggesting that this species is already in circulation in Europe.

The introduction of exotic *Leishmania* species or strains in areas of Europe where the vectors are well established and circulating the local parasites, may increase the chance of genetic exchange between them [12]. As a result, new hybrids could be generated characterized by different infectivity for sand fly species or different pathogenicity for the vertebrate hosts, a situation already evidenced with *L. infantum*/*L. major* hybrids [94].

4. Conclusion

The epidemiological complexity of sand fly-borne infections in Europe is changing and likely to increase, as suggested by the discovery of new pathogens, new potential reservoir hosts and vectors, new cycles of transmission, the geographical spread of endemicity and the increase of susceptible populations. Global phenomena influencing these changes include anthropogenic factors associated with climate and human-made changes and increased movements of animals and people through tourism and migration.

The challenges and threats identified reinforce the need to implement mandatory notification of human and canine leishmaniases and phleboviruses in endemic and non-endemic countries, and coordinated epidemiological surveillance at European level, including monitoring the distribution of sand flies and detection of the agents transmitted by them, both in vectors and in vertebrate hosts. Finally, it is important to increase awareness among healthcare professionals and the public about diseases transmitted by sand flies, following a One Health approach.

Funding

This work was in part supported by Fundação para a Ciência e a Tecnologia (GHTM - UID/04413/2020 and LA-REAL – LA/P/0117/2020), the European Commission (grant 101057690) and UK Research and Innovation (grants 10038150 and 10039289), and is catalogued by the CLIMOS Scientific Committee as CLIMOS number 001 (http://www.climos-project.eu). The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

Author statement

The contents of this publication are the sole responsibility of the author and do not necessarily reflect the views of the European Commission, the Health and Digital Executive Agency or UK Research and Innovation (UKRI). Neither the European Union, the granting authority nor UKRI can be held responsible. For the purposes of Open Access, the author has applied a CC BY-ND public copyright licence to any Author Accepted Manuscript version arising from this submission. The six Horizon Europe projects, BlueAdapt, CATALYSE, CLIMOS, HIGH Horizons, IDAlert and TRIGGER, form the Climate Change and Health Cluster.

Statement of author's contribution

C. Maia: Conceptualization; Investigation; Writing – original draft, reviewing and editing; Visualization.

Declaration of competing interests

The author declared no potential conflicts of interest with respect to the research, authorship or publication of this article.

Acknowledgments

The author acknowledges receipt of the 2023 *Journal of Comparative Pathology* keynote lecturer award at the 2023 European Society of Veterinary Pathology–European College of Veterinary Pathologists annual congress. A summary of this review was delivered as a plenary lecture at the second joint Congress of Veterinary Pathology and Veterinary Clinical Pathology (ESVP/ECVP/ESVCP/ECVCP), which took place from the 31st August to 2nd September 2023 in Lisbon, Portugal.

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