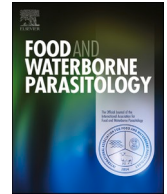




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Multiscale ecological drivers of *Echinococcus multilocularis* spatial distribution in wild hosts: A systematic review

Andrea Simoncini^a, Alessandro Massolo^{b,c,d,*}

^a Dipartimento di Scienze e Politiche Ambientali, Università degli Studi di Milano, Milano 20133, Italy

^b Dipartimento di Biologia, Università di Pisa, Pisa 56121, Italy

^c Faculty of Veterinary Medicine, University of Calgary, Calgary, Alberta T2N 1N4, Canada

^d UMR CNRS 6249 Chrono-environnement, Université Franche-Comté, Besançon 25030, France

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ABSTRACT

Understanding the ecological factors that drive the spatial patterns of parasites transmission is essential to predict their distribution under global change and to direct proactive surveillance efforts. Here, we systematically reviewed the literature to assess the main ecological drivers responsible for the spatial distribution and transmission of the zoonotic cestode *Echinococcus multilocularis*, the aetiological agent of alveolar echinococcosis, focusing on wild hosts. The 23 retrieved studies suggested that the dispersal of definitive hosts, climatic and biotic factors (distribution of intermediate hosts, composition of host communities) shape continental-scale distribution patterns of *E. multilocularis*, whereas the relative importance of climate and land cover in driving *E. multilocularis* distribution at a smaller (country/regional) scale varies with the geographic area considered. At a local scale, two additional factors contribute to determine the distribution of micro-foci of transmission: the trophic relationships between carnivores definitive hosts and small mammals intermediate hosts, and the defecation and marking behaviour of definitive hosts.

1. Introduction

Echinococcus multilocularis (Leuckart 1863) is a taeniid cestode responsible for alveolar echinococcosis (AE) in humans, the most important food-borne disease in Europe (Bouwknegt et al., 2018). It has a complex sylvatic life cycle involving canids as definitive hosts (foxes in the genera *Alopex* and *Vulpes*, wolves *Canis lupus*, coyotes *C. latrans*, raccoon dogs *Nyctereutes procyonides* and small mammals (primarily arvicoline and cricetid rodents and lagomorphs) as intermediate hosts (Romig et al., 2017). A domestic life cycle can also occur involving feral and domestic dogs and cats as definitive hosts (Thompson and Jenkins, 2014). Several species can then act as ‘dead-end’ or aberrant hosts as the domestic pig, the wild boar and humans (Romig et al., 2017). The intermediate host is the stage at which the parasite is more virulent, as it undergoes a tumor-like growth primarily in the liver that often results in the host death (Torgerson et al., 2010; Vuitton et al., 2015).

The geographic range of *E. multilocularis* extends throughout the northern hemisphere with the main endemic regions located in Europe (Austria, Switzerland, Germany, France, eastern Europe - Deplazes et al., 2017), Asia (China - Torgerson et al., 2010) and North America (Massolo et al., 2014). A range expansion has been extensively documented in Europe and across the Northern Hemisphere in

* Corresponding author at: Dipartimento di Biologia, Unità di Etologia, Università di Pisa, Via Volta 6, Pisa 56121, Italy.

E-mail address: alessandro.massolo@unipi.it (A. Massolo).

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the last thirty years (Davidson et al., 2012; Beck et al., 2018; Dan et al., 2018).

Understanding the ecological factors that drive the spatial patterns of occurrence and transmission of this parasite is essential to direct surveillance efforts and to predict the expected changes of its distribution under global change (Atkinson et al., 2013; Johnson et al., 2019). Furthermore, it is known that transmission intensity of *E. multilocularis* varies remarkably in space (Beerli et al., 2017), and this variation occurs over a wide range of spatial scales, from local (even hundreds of meters; Beerli et al., 2017) to continental (Europe - Oksanen et al., 2016; Cenni et al., 2023, Asia - Danson et al., 2003). For example, human contamination with *E. multilocularis* in China has been correlated to changes in climatic conditions over large areas that in turn drive the distribution of different landscapes, characterized by different communities of intermediate hosts and hence different abilities to sustain *E. multilocularis* (Danson et al., 2003). On the other side, Tackmann et al., 1998 evidenced the presence of a heterogeneous distribution of *E. multilocularis* in foxes at a fine spatial scale in northwestern Brandenburg, Germany, and noted a decrease of infection in a 26 km range moving away from a local focus.

A systematic review investigating the epidemiology of *E. multilocularis* transmission in wild and domestic animals, published by Otero-Abad and Torgerson, 2013, provided a general overview of the main drivers of infection intensity and distribution of *E. multilocularis*, but they did not emphasize the different spatial scales at which each factor operates and did not mention behavioural traits as relevant drivers of *E. multilocularis* transmission besides a short note on the role of predation and feeding ecology. Furthermore, they also focused on within-population differences in infection intensity, trying to disentangle the factors contributing to explain the observed differences in infection intensity between age classes or sexes, whereas we focused more on spatial differences. In the same year, Atkinson et al., 2013, provided a conceptual diagram of the influence of several ecological factors on *E. multilocularis* transmission risk and reviewed the literature on global change and *Echinococcus* transmission. However, they did not account for the different spatial scales at which the drivers of *Echinococcus* distribution operate and focused primarily on the predicted effects of global change rather than on the underlying ecological processes driving species' distribution.

A review by Raoul et al., 2015, focused instead on the role of trophic ecology and behaviour in *E. multilocularis* transmission, considering only field-based studies. Massolo et al., 2022 hypothesized that the broad-scale distribution of *E. multilocularis* is driven by the shorter life span of the intermediate hosts and the higher virulence of the larval stage of this parasite compared to congeneric species, that prevent the colonization of arid environments as the parasite cannot survive long periods of drought inside long-lived intermediate hosts.

In this work, we aimed to: i) expand on the existing reviews by providing a coherent synthesis of environmental (climate, land cover, geomorphology), biotic (host distribution and communities), and behavioural (trophic ecology, defecation behaviour) drivers of *E. multilocularis* transmission and distribution; ii) account for the spatial scale(s) at which the drivers of *E. multilocularis* transmission operate; iii) update previous reviews with data from more recent studies (devoting more attention to studies published after the aforementioned reviews), to help track and synthesize the growing number of papers issued on *E. multilocularis* ecology.

2. Methods

2.1. Literature search

To search the literature, we followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (Page et al., 2021). Web of Science, Scopus and PubMed databases were searched in the title, abstract and keywords fields with the following search string: '*Echinococcus multilocularis*' AND ('Distribut*' OR 'Transmi*'). The final search was performed on June 26th, 2023.

2.2. Selection criteria and articles screening

To exclude papers that did not investigate the ecological drivers of *E. multilocularis* spatial distribution and transmission, we first performed a screening based on the title and abstract of the studies retrieved from the search. The full text was then read for the retained papers and the compliance with three inclusion criteria was verified: (C1) *E. multilocularis* is detected in sylvatic hosts, (C2) the spatial variation in the occurrence/transmission of *E. multilocularis* is related to the variation in space of ecological drivers, (C3) the geographic location of the study is reported.

We focused on sylvatic hosts as *E. multilocularis* is primarily maintained in a sylvatic cycle, and spillovers from wild hosts to domestic ones are often involved although transmission to humans differs according to the continent and the prevalence of the parasite in dogs (Paternoster et al., 2021). Moreover, humans and domestic animals are highly mobile and associations between spatial predictors and georeferenced records of *E. multilocularis* infections might be mismatched if the infection had been acquired in a different place. Furthermore, free-roaming domestic dogs and domestic cats do not excrete the eggs of *E. multilocularis* as much as sylvatic hosts (e.g., the red fox *Vulpes vulpes*; Kapel et al., 2006), and the prevalence of the parasite in these hosts is significantly lower (Bastien et al., 2018), with the exception of Asia where dogs contribute significantly to the transmission of the parasite (Toews et al., 2021).

Once the screened papers were obtained, data were extracted concerning the location, the spatial scale of the study, the sylvatic species found infected, the ecological drivers used as independent variables and the direction of their effect on *E. multilocularis* spatial distribution and transmission. Ecological drivers were broadly defined as climatic, land cover, geomorphological, behavioural or biotic variables. As most studies did not report a precise measure of the spatial extent of the studied area, the spatial scale was attributed according to four qualitative levels: local, regional, country, continental of increasing spatial extent. To reduce the plethora of ecological drivers to a smaller set, variables referring to average temperatures over different time scales (e.g., 1 year or 30 year means)

were grouped in the single predictor ‘Average temperatures’ and the same was applied for precipitations (single predictor ‘Average precipitations’). Effects were classified as either positive, negative, asymptotic, unimodal or other (e.g., logistic, bimodal). From each study we collected the following data: i) first author, ii) year, iii) country/region, iv) wild host(s), v) ecological driver(s), vi) direction of its/their effect(s) on *E. multilocularis* transmission, vii) spatial scale(s).

3. Results

Our search retrieved 1724 papers, of which 685 were duplicates, resulting in 1039 screened articles (Fig. 1). Of these, 993 articles were excluded based on their title and abstract, and for 8 of the retained articles it was not possible to retrieve the full text, resulting in 38 reports who were fully investigated to check the agreement with the defined inclusion criteria. For 15 of these papers at least one of the inclusion criteria was not met, hence we finally obtained 23 papers that investigated the relationship between ecological drivers and *E. multilocularis* distribution and transmission explicitly accounting for space (Fig. 1; Table 1). Most studies modelled real data, whereas theoretical simulations were only used in two cases (Table 1). Twenty-one ecological predictors were used in these studies, with ‘Average temperatures’, ‘Average precipitations’ and ‘Urban cover’ being the most investigated (four studies each; Table 2). The effects of these variables were estimated to be consistently negative and positive for average temperatures and average precipitations,

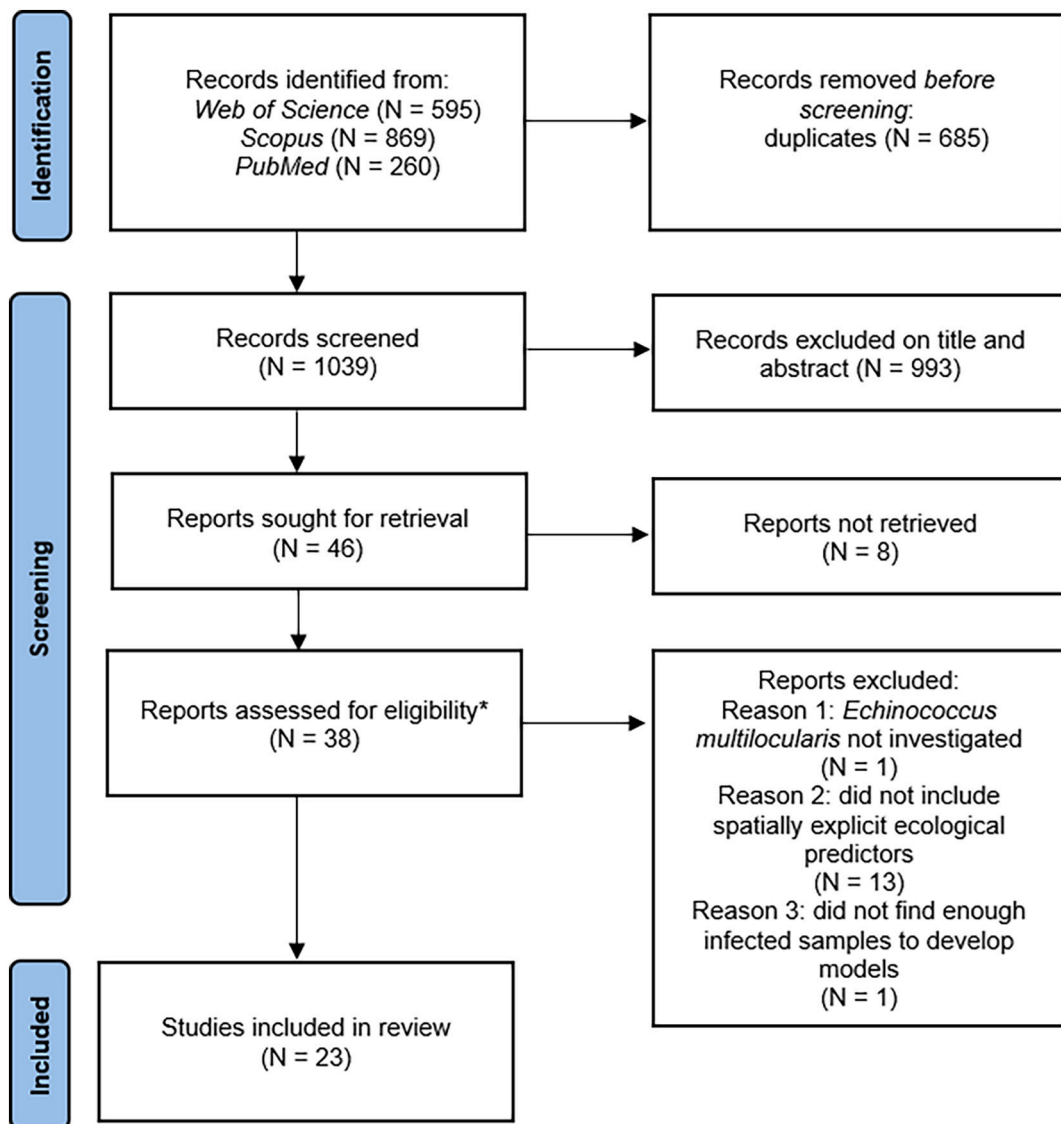


Fig. 1. Flow chart of the systematic search according to the PRISMA guidelines (Page et al., 2021). *Inclusion criteria: (C1) *Echinococcus multilocularis* is detected in sylvatic hosts, (C2) the occurrence/transmission of *E. multilocularis* is related to spatially explicit ecological drivers, (C3) the geographic location of the study is reported.

Table 1

Summary of studies that relate *Echinococcus multilocularis* occurrence, prevalence or intensity of infection in wild hosts with ecological predictors, ordered from the larger to the smaller spatial scale. Species reported are those infected and whose infection was therefore related to ecological predictors; the study might have included other species. **Arvicola terrestris*, *Arvicola amphibius* and *Arvicola scherman* should be considered as synonym, although their taxonomy is still debated (Kryštufek et al., 2015).

N	First author	Year	Country, region	Scale	Wild IH	Wild DH
1	Takeuchi-Storm	2015	All (meta-analysis)	Continental	<i>Apodemus</i> , <i>Arvicola</i> , <i>Microtus</i> , <i>Myodes</i> , <i>Ondatra</i>	<i>Vulpes vulpes</i>
2	Botero-Cañola	2019	North America	Continental	<i>Lemmus trimacronatus</i> , <i>Microtus oeconomus</i> , <i>Microtus pennsylvanicus</i> , <i>Mus musculus</i> , <i>Myodes gapperi</i> , <i>Ondatra zibethicus</i> , <i>Peromyscus maniculatus</i>	<i>Canis latrans</i> , <i>Canis lupus</i> , <i>Vulpes vulpes</i> , <i>Vulpes lagopus</i>
3	Cenni	2023	Europe	Continental	–	<i>Vulpes vulpes</i>
4	Miterpáková	2006	Slovak Republic	Country	–	<i>Vulpes vulpes</i>
5	Casulli	2010	Hungary	Country	–	<i>Vulpes vulpes</i>
6	Tolnai	2013	Hungary	Country	–	<i>Vulpes vulpes</i>
7	Miller	2017	Sweden	Country	<i>Arvicola amphibius</i> *, <i>Microtus agrestis</i>	<i>Vulpes vulpes</i>
8	Pleydell	2004	Franche-Comté region, France	Regional	–	<i>Vulpes vulpes</i>
9	Raoul	2010	Franche-Comté and Burgundy regions, France	Regional	<i>Arvicola terrestris</i> *	<i>Vulpes vulpes</i>
10	Bastien	2018	Ardennes, France	Regional	<i>Arvicola amphibius</i> *, <i>Apodemus</i> sp., <i>Microtus</i> sp., <i>Myodes glareolus</i>	<i>Vulpes vulpes</i>
11	Kotwa	2020	Southern Ontario, Canada	Regional	–	<i>Canis latrans</i>
12	Avcioglu	2021	Erzurum region, Turkey	Regional	–	<i>Vulpes vulpes</i>
13	Staubach	2001	Northwest of Brandenburg, Germany	Local	–	<i>Vulpes vulpes</i>
14	Stieger	2002	Zürich, Switzerland	Local	–	<i>Vulpes vulpes</i>
15	Hansen	2004	Simulated landscape	Local	<i>Microtus arvalis</i>	<i>Vulpes vulpes</i>
16	Fuglei	2008	Spitsbergen, Svalbard	Local	<i>Microtus levis</i>	<i>Vulpes lagopus</i>
17	Stien	2010	Spitsbergen, Svalbard	Local	<i>Microtus levis</i>	<i>Vulpes lagopus</i>
18	Burlet	2011	Zürich, Switzerland	Local	<i>Arvicola terrestris</i> *	–
19	Robardet	2011	Nancy, France	Local	<i>Arvicola terrestris</i> *	<i>Vulpes vulpes</i>
20	Guerra	2014	Canton of Ticino, Switzerland	Local	<i>Arvicola amphibius</i> *, <i>Chionomys nivalis</i> , <i>Microtus arvalis</i> , <i>Microtus multiplex</i> , <i>Microtus savii</i> , <i>Microtus subterraneus</i> , <i>Myodes glareolus</i>	<i>Vulpes vulpes</i>
21	Otero-Abad	2017	Zürich, Switzerland	Local	–	<i>Vulpes vulpes</i>
22	Mori	2019	Calgary, Canada	Local	<i>Peromyscus maniculatus</i> , <i>Microtus pennsylvanicus</i> , <i>Sorex</i> sp., <i>Myodes gapperi</i> , <i>Zapus princeps</i> , <i>Spermophilus tridecemlineatus</i> , <i>Tamias minimus</i> , <i>Thomomys talpoides</i> , <i>Mus musculus</i>	<i>Canis latrans</i>
23	Mori	2023	Calgary (simulated), Canada	Local	<i>Microtus pennsylvanicus</i> , <i>Peromyscus maniculatus</i> , <i>Myodes gapperi</i>	<i>Canis latrans</i>

respectively, and primarily positive for urban cover (Table 2). The most investigated spatial scale was the local (11 studies out of 23; Table 2), and only two studies were carried out at a continental scale and employed species distribution models to predict the current and future distribution of *E. multilocularis* (Table 3). The effect of precipitations and humidity on the spatial distribution of the parasite was generally positive across different spatial scales and the effect of temperature was generally negative (Fig. 2). The effect of other predictors was variable across the different spatial scales, except for the presence of water bodies that showed a positive influence on *E. multilocularis* occurrence both at the local and the country scales and the forest cover that had a negative effect over the same two spatial scales (Fig. 2). The selected studies did not provide redundant information, i.e., studies at a wider spatial scale did not present the data from smaller spatial scale studies, with the possible exception of the meta-analysis by Takeuchi-Storm et al., 2015.

4. Discussion

Through a systematic search of the literature, we identified 23 papers that related the spatial distribution and transmission of *E. multilocularis* to ecological drivers.

4.1. Climate

The relevance of climate as a driver of *E. multilocularis* distribution has long been suggested; for example, Shaikenov, 2006, noted that in Central Asia the number of endemic foci of *E. multilocularis* transmission increased from desertic to steppic ecosystems and also noted that *E. multilocularis* was found primarily in humid small-scale habitats in the most arid regions. In France, there is no evidence of *E. multilocularis* presence in areas with an average annual temperature higher than 12 °C (Giraudoux et al., 2013). Hansen et al., 2004, developed simulations to explain the heterogeneous distribution of *E. multilocularis* infection in intermediate hosts and out of five

Table 2

Ecological drivers of *Echinococcus multilocularis* spatial distribution and transmission in wild hosts reported in the literature. Positive (+ corr) and negative (– corr) correlations of ecological drivers with the occurrence, prevalence or intensity of infection with *E. multilocularis* are reported, together with asymptotic, unimodal or other (Assoc) relationships. Numbers indicate the following references: ¹Staubach et al., 2001, ²Stieger et al., 2002, ³Hansen et al., 2004, ⁴Pleydell et al., 2004, ⁵Miterpakova et al., 2006, ⁶Fuglei et al., 2008, ⁷Casulli et al., 2010, ⁸Raoul et al., 2010, ⁹Stien et al., 2010, ¹⁰Burlet et al., 2011, ¹¹Robardet et al., 2011, ¹²Tolnai et al., 2013, ¹³Guerra et al., 2014, ¹⁴Takeuchi-Storm et al., 2015, ¹⁵Miller et al., 2017, ¹⁶Otero-Abad et al., 2017, ¹⁷Bastien et al., 2018, ¹⁸Botero-Cañola et al., 2019, ¹⁹Mori et al., 2019, ²⁰Kotwa et al., 2020, ²¹Avcioglu et al., 2021, ²²Cenni et al., 2023, ²³Mori et al., 2023. The spatial scale(s) of the studies that report an association with a given factor is/are also reported.

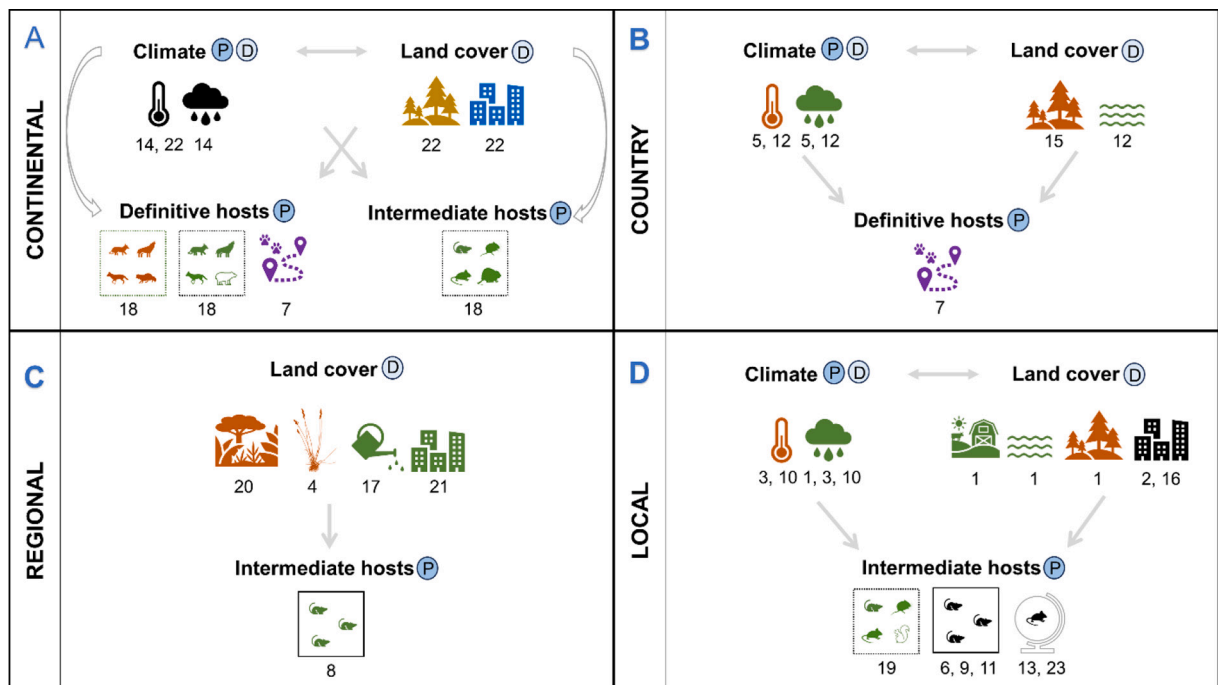
Variable	+ corr	- corr	Assoc	Asymptotic	Unimodal	Scale(s)
Average temperatures		3, 5, 10, 12				Local, country
Maximum daily temperature warmest month		14				Continental
Mean temperature coldest quarter					22	Continental
Average precipitations	5, 10, 12, 14					Local, country, continental
Average precipitations driest month		14				Continental
Average precipitations wettest month		14				Continental
Presence of water bodies	1, 12					Local, country
Humidity	1, 3, 5					Local, country
Grassland cover				4		Regional
Pastures cover	1					Local
Forest cover		1, 15			22	Local, country, continental
Urban cover	21	2	16	22		Local, regional, continental
Intermediate hosts richness	18					Continental
Intermediate hosts proportion	19					Local
Intermediate hosts distribution	13		23			Local
Intermediate hosts density	6, 8, 9	11				Local, regional
Definitive hosts richness		18				Continental
Definitive hosts proportion	18					Continental
Definitive hosts dispersal			7			Country, Continental
Proportion of natural land cover in home range		20				Regional
Presence of kitchen gardens	17					Regional

Table 3

Variables employed in the two continental-scale species distribution models that relate *Echinococcus multilocularis* occurrence in wild hosts to ecological predictors: Botero-Cañola et al., 2019 predicted *E. multilocularis* occurrence in North America while Cenni et al., 2023 predicted *E. multilocularis* occurrence in Europe. The permutation importance of each variable expressed as percentage contribution is reported. In both studies, permutation importance was obtained in the Maxent software by randomly permuting the values of a given variable at the points used to develop the model and assessing the decrease in predictive performance on the same points; large decreases are indicators of important variables. Percentage values were then obtained by normalization.

Variable	Botero-Cañola et al., 2019	Cenni et al., 2023
Average daily solar radiation	7.2	–
Precipitation of wettest month	0.6	2.5
Precipitation of driest month	0.2	–
Precipitation seasonality	–	6.8
Max temperature of warmest month	9.4	–
Mean temperature of coldest quarter	–	59.2
Temperature annual range	1.0	1.5
Precipitation seasonality	3.7	–
Definitive host proportion	22.0	–
Definitive host richness	34.3	–
Intermediate host richness	17.4	–
Intermediate host proportion	4.3	–
Forest cover	–	11.0
Urban cover	–	8.5
Open areas	–	3.5
Roughness	–	6.6
Topographic Position Index	–	0.3

possible scenarios the most supported one accounted for the differential mortality of eggs in the environment linked to climatic conditions. Miterpakova et al., 2006, sampled 3096 red foxes in the Slovak Republic and related the prevalence of *E. multilocularis* infection to environmental factors. Foci with a high prevalence (> 30%) were found in areas with lower mean annual air temperature and higher mean annual rainfall. Burlet et al., 2011, found that low temperatures were significantly correlated with *E. multilocularis* infection in *Arvicola amphibius* at a local scale in Zürich, Switzerland. Tolnai et al., 2013, found that the heterogeneous spatial distribution of *E. multilocularis* in Hungary was primarily related to the mean annual temperature and annual precipitation. In a meta-analysis investigating the drivers of *E. multilocularis* prevalence, Takeuchi-Storm et al., 2015, found that three out of four tested climatic drivers had a significant influence in explaining *E. multilocularis* infection in definitive hosts. A negative relationship between the



	Temperature		Pasture		DH density
	Precipitation/Humidity		Urban		DH proportion
	Water bodies		DH* dispersal		IH richness
	Kitchen gardens		IH** distribution		+ correlation
	Natural habitat		DH density		- correlation
	Forest		DH proportion		Unimodal
	Grass		DH richness		Asymptotic
					Other
					More than one
					Proximal driver
					Distal driver

*DH = Definitive Host, **IH = Intermediate Host

Fig. 2. Ecological drivers of *Echinococcus multilocularis* spatial distribution in wild hosts across multiple spatial scales: (A) continental, (B) country, (C) regional, (D) local. Arrows indicate interactions between general drivers (climate, land cover, definitive hosts, intermediate hosts) and icons represent specific drivers (e.g., temperature, cover of forests). Icon colours indicate the direction of the effect (dark green: positive correlation, dark orange: negative correlation, blue: unimodal, brown: asymptotic, purple: other association, black: more than one association). P and D icons indicate proximal (i.e., direct) and distal (i.e., mediated by one or more other factors) effects on the distribution of *E. multilocularis*, respectively. Numbers below icons indicate the following references: ¹Staubach et al., 2021, ²Stieger et al., 2002, ³Hansen et al., 2004, ⁴Pleydell et al., 2004, ⁵Miterpáková et al., 2006, ⁶Fuglei et al., 2008, ⁷Casulli et al., 2010, ⁸Raoul et al., 2010, ⁹Stien et al., 2010, ¹⁰Burlet et al., 2011, ¹¹Robardet et al., 2011, ¹²Tolnai et al., 2013, ¹³Guerra et al., 2014, ¹⁴Takeuchi-Storm et al., 2015, ¹⁵Miller et al., 2017, ¹⁶Otero-Abad et al., 2017, ¹⁷Bastien et al., 2018, ¹⁸Botero-Cañola et al., 2019, ¹⁹Mori et al., 2019, ²⁰Kotwa et al., 2020, ²¹Avcioglu et al., 2021, ²²Cenni et al., 2023, ²³Mori et al., 2023. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

driver and prevalence in definitive hosts was found for average precipitation of the wettest month, average precipitation of the driest month and average maximum daily temperature of the warmest month, whereas a positive relationship was detected for average annual precipitation. When modelling the distribution of *E. multilocularis* at a continental scale in North America, Botero-Cañola et al., 2019, found that average daily solar radiation and the maximum temperature of the warmest month were the two most relevant predictors according to the jackknife test. Solar radiation was related to the probability of occurrence with a peak of suitability for the parasite at intermediate levels, whereas a positive relationship with the maximum temperature of the warmest month was detected

(Botero-Cañola et al., 2019). Cenni et al., 2023, modelled the distribution of *E. multilocularis* in Europe as a function of a set of ecological predictors, contrasting seven alternative models built with different sets of predictors. The variable with the highest contribution in the best supported model was the mean temperature of the coldest quarter (Table 3), with a unimodal relationship with maximum values comprised between -10°C and 10°C , suggesting the preference for cold temperatures and a crucial role of temperature in shaping the distribution of the parasite at a continental scale (Fig. 2).

The link of *E. multilocularis* distribution with temperature, humidity and precipitation is primarily explained by the effect of these parameters on egg survival and the distribution and co-occurrence patterns of definitive and intermediate hosts (Danson et al., 2003; Shaikenov, 2006). Indeed, *E. multilocularis* eggs are highly sensitive to high temperatures and desiccation, as proved experimentally by (Veit et al., 1995). In these experiments, the eggs died within 2 h independently from the humidity if exposed to temperatures of 43°C , and died within two days if exposed to 25°C at a 27% of relative humidity (Veit et al., 1995). Also, the negative impact of a very high solar radiation on *E. multilocularis* distribution at large scales might be related to the negative effect of ultraviolet radiations on egg survival (Veit et al., 1995; Botero-Cañola et al., 2019). Comparing studies from different countries it appears that the relative contribution of climate as a driver of *E. multilocularis* occurrence is variable, e.g., in Hungary climatic variation is more relevant compared to Germany, where land cover has been shown to be more important (Tolnai et al., 2013). This variation might also be explained by the wide variation in spatial extent between different countries. Climatic variables also drive host distributions and density via their influence on vegetation patterns and land cover in general (Danson et al., 2003; Takeuchi-Storm et al., 2015).

4.2. Land cover

Land cover is a key driver of *E. multilocularis* transmission primarily through its effect on intermediate hosts distribution, as rodents' population dynamics and community composition are affected by land cover type, via its influence on food availability and cover from predators (Fig. 2; Kotwa et al., 2020). Furthermore, the prevalence of *E. multilocularis* in foxes has been related to the presence of landscapes conducive to rodent population outbreaks (Guislain et al., 2007). Also, Mori et al., 2019, demonstrated that land cover can act as a reliable proxy to predict *E. multilocularis* intermediate host assemblages also in a city setting (Calgary, Alberta, Canada).

4.2.1. Grassland and agriculture

In Brandenburg, Germany, Staubach et al., 2001, described an increased number of infected foxes in open landscapes compared to forested ones. Pleydell et al., 2004, found an asymptotic relationship between *E. multilocularis* infection in foxes and grassland cover in France up to a 35% threshold grassland ratio, beyond which a plateau was reached. In Germany and France, the countries investigated in these studies, two main terrestrial intermediate hosts occur (*Microtus arvalis*, *A. terrestris*), and it has been hypothesized that the preference for grasslands of the fossorial populations of *A. terrestris* might drive the relationship between grassland cover and *E. multilocularis* presence (Tolnai et al., 2013). Besides, grassland percentage is a variable that can partly explain rodent outbreaks (Giraudoux et al., 2002).

4.2.2. Forest

A negative relationship between the occurrence of *E. multilocularis* in foxes and the amount of forest cover was detected on a local scale by Staubach et al., 2001, in Germany. Miller et al., 2017, found that rodents in Sweden from forest habitats were more likely to be parasitized than rodents in field habitats, and Kotwa et al., 2020, in southern Ontario detected a negative relationship between the infection of *E. multilocularis* in coyotes and the proportion of natural land cover in their home ranges. As natural land cover in southern Ontario is primarily represented by forested landscapes, this relationship suggests a negative effect of forest cover on *E. multilocularis* infection in the canid definitive host at a regional scale. Finally, Cenni et al., 2023, documented a unimodal relationship between forest cover and *E. multilocularis* occurrence probability at the continental scale in Europe, with maximum suitability values comprised between 40% and 60% cover.

From all these studies, it appears that forest cover generally exerts a negative influence on *E. multilocularis* presence across all spatial scales (Fig. 2). However, the finding of an asymptotic relationship between occurrence and grasslands found by Pleydell et al., 2004, and the unimodal relationship with forest cover peaking at intermediate levels found by Cenni et al., 2023, suggest that landscapes with a mixed presence of open and forested areas might be the most conducive for transmission.

4.2.3. Urban areas

The presence of *E. multilocularis* in urban contexts is increasingly recognized and documented from several cities across the Holarctic (e.g., Zurich, Geneva, Stuttgart, Copenhagen, Sapporo, Nancy, Calgary; Massolo et al., 2014; Raoul et al., 2015). Stieger et al., 2002, found that the proportion of positive fox faeces increased from the urban to the periurban zone in Zürich, Switzerland. In the same city, Burlet et al., 2011, detected micro-foci of *A. terrestris* infection with *E. multilocularis* (prevalence: 95% CI 40.6–78.5%) in densely populated areas within the urban matrix, whereas other studied sites had lower prevalence values indicating a relevant positive effect of urbanization on infection in intermediate hosts. In Nancy, France, Robardet et al., 2011, found that *Microtus* species were aggregated in urban wasteland, and described this as a mechanism driving the occurrence of infected foxes in these areas. Otero-Abad et al., 2017, attempted to explain the spatial differences in fox infection pressure across different urban types in Zürich, and found that transmission was higher in city outskirts and peripheral areas for young foxes whereas the opposite held true for adults. Avcioglu et al., 2021, found that red foxes and their faeces from the most central districts of Erzurum in Turkey harboured more *E. multilocularis* than foxes and fox faeces from the peripheral districts. Over a continental scale in Europe, Cenni et al., 2023, detected an asymptotic relationship between *E. multilocularis* occurrence in red foxes and the percentage of urban cover.

The association of *E. multilocularis* with urban areas has been detected from local to continental scales and might be related to increased definitive hosts densities in urban compared to rural areas (Robardet et al., 2011). Besides, the increased urban sprawl and development in historically endemic rural areas, e.g., in central Europe, might contribute to explain the presence of *E. multilocularis* in cities (Knapp et al., 2018). The increased transmission in peripheral city areas appears to reflect a greater consumption of rodents in these areas compared to the city centers where more alternative resources are available to the definitive hosts (Otero-Abad et al., 2017). Studies that found an opposite trend (i.e., highest infection in the city center) might be biased by the presence of super infected foxes that died in the city center after feeding on the city outskirts (Otero-Abad et al., 2017). Local foci of transmission might nevertheless occur inside cities due to the particular abundance of rodents (e.g., in wastelands; Robardet et al., 2011) or conducive abiotic conditions (e.g., kitchen gardens are watered throughout the summer and might therefore allow egg survival compared to other micro-habitats within the city; Bastien et al., 2018).

Previous reviews synthesizing knowledge on urban transmission of *E. multilocularis* have highlighted a complex interplay of several drivers: the density of the human population and of the definitive hosts, the spatial and foraging behaviour of the definitive hosts, the abundance of intermediate hosts, the spatial patterns of human activities, the density of free-roaming dogs and cats and landscape features (Deplazes et al., 2004; Liccioli et al., 2015). Among these factors, the interplay between landscape features and the abundance of intermediate hosts appears to be critical, as the proportion of optimal habitat for small mammals is deemed to be one of the main drivers of *E. multilocularis* transmission. Besides, as the configuration of urban landscapes is heterogeneous, it has been noted that different gradients of urban density and different connectivity with green areas shape the transmission of the parasite (Liccioli et al., 2015).

4.2.4. Water bodies

Staubach et al., 2001, in Brandenburg, Germany, found that foxes infected with *E. multilocularis* were shot near water bodies more frequently, and the presence of water bodies has been mentioned as a critical factor for the transmission of this cestode in Central Asia by Shaikenov, 2006. In Hungary, Tolnai et al., 2013, recorded a higher number of water bodies inside the home ranges of red foxes infected with *E. multilocularis* compared to uninfected ones.

The increase in suitability for *E. multilocularis* with the presence of water bodies may be related to the enhanced egg survival in humid environments (Veit et al., 1995) and to the occurrence of intermediate hosts critical for the life cycle of the parasite, e.g., *Ondatra zibethicus* (Tolnai et al., 2013).

4.3. Soil

As the eggs of *E. multilocularis* are spread in the environment with faeces, the soil can be contaminated and acts as a critical vector of infections (Da Silva et al., 2021). Studying soil contamination instead of faeces might help to detect *E. multilocularis* even when faeces have deteriorated, increasing the reliability of estimates of the spatial distribution and occurrence of the parasite (Da Silva et al., 2021). A positive relationship between soil humidity and *E. multilocularis* occurrence probability was found by Staubach et al., 2001, in Germany. Soil moisture was suggested as a relevant predictor by Burlet et al., 2011, that failed to predict *E. multilocularis* occurrence based on precipitation values and remarked that soil moisture has a direct effect on egg survival and depends not only on precipitation but also on several other parameters (e.g., vegetation growth and temperature). In 2013, Tolnai et al., 2013, tested the role of soil water retention and soil permeability on the infection status with *E. multilocularis* of red foxes in Hungary, failing to detect any significant relationship. Techniques to detect *E. multilocularis* in soils have only recently improved (Da Silva et al., 2021). Therefore, further studies evaluating egg survival in different soil types while accounting for the potential impact of vegetation cover are required.

4.4. Topography

Few studies have investigated the effect of geomorphological variables on the transmission of *E. multilocularis*. Tolnai et al., 2013, found a highly significant positive correlation between fox home range altitude and infection intensity in Hungary, but multicollinearity with temperature was detected using a multiple regression analysis. Cenni et al., 2023, tested the ability of several geomorphological variables to predict *E. multilocularis* distribution in Europe at a continental scale, but none of them proved useful (Table 3).

4.5. Behaviour and trophic ecology

4.5.1. Definitive host dispersal

Spatially explicit studies of *E. multilocularis* genetic diversity over large spatial scales have detected a lower genetic diversity in areas colonized more recently by the definitive hosts, e.g., the genetic diversity of the parasite was lower in red foxes from south-eastern Hungary compared to north-western Hungary (Casulli et al., 2010). Casulli et al., 2010, strongly advocate that this pattern of genetic variation is related to the dispersal movement of red foxes that spread the parasite across different countries in a short timespan, leading to a consistent genetic drift. Also findings from other studies not retrieved by our systematic search protocol suggest that definitive hosts dispersal might contribute to spread the parasite over large areas (Knapp et al., 2009; Hagenlund et al., 2019).

4.5.2. Definitive host defecation behaviour

The heterogeneous distribution of red fox faeces has been advocated as a mechanism driving the emergence of micro-foci of

E. multilocularis transmission (Giraudoux et al., 2002). The home ranges of infected foxes would also act as a spatial limit driving the faecal distribution and the heterogeneous contamination of the environment and of intermediate hosts (Pleydell et al., 2004). Guislain et al., 2007, provided for the first time evidence of the spatial clustering of both intermediate host and red fox faeces in north-eastern France. Robardet et al., 2011 in Nancy, France, described an increase in red fox faecal deposits in transects with a higher density of voles. Bastien et al., 2018, related the prevalence of *E. multilocularis* in rodents and the density of fox faeces within and outside kitchen gardens in the Ardennes, France, and found an increased prevalence in rodents from kitchen gardens. They also found the density of fox faeces in kitchen gardens to be comparable with the one observed in habitat edges, traditionally regarded as habitats where faecal deposits from red foxes are highly abundant (Bastien et al., 2018).

The effect of faecal deposition on *E. multilocularis* transmission is detectable at a local scale, and the actual fine-scale foci of transmission occur at the intersection of the home ranges of intermediate hosts and the definitive hosts faecal deposits (Guislain et al., 2007). Transmission is therefore enhanced by the defecation and marking behaviour of definitive hosts that release contaminated faeces soon after feeding, therefore increasing the match between intermediate host spatial occurrence and the distribution of contaminated material (Robardet et al., 2011).

4.5.3. Trophic ecology

The predation of definitive hosts on intermediate host is a critical factor in the epidemiology of trophically-transmitted parasites (Raoul et al., 2015). In particular, the functional response of predators to variations in prey densities and abundance has been shown to be critical in *E. multilocularis* transmission (Raoul et al., 2015). Indeed, the parasite transmission is enhanced where and when there is a high density of certain small mammal species that are dominant in the fox diet, e.g., *Microtus oeconomus* on St. Lawrence island, or *A. terrestris* and *M. arvalis* in France and Switzerland (Guislain et al., 2008). Raoul et al., 2010, detected a sigmoidal response of fox contamination with *E. multilocularis* in relationship to an increased density of *A. terrestris*. However, Liccioli et al., 2014, found that the relative composition of prey communities, rather than the abundance of specific species, affected the transmission of *Echinococcus multilocularis* in the city of Calgary, Canada. A possible explanation for this phenomenon might be the variation of preferential food items following variations in the relative densities of competent and non-competent intermediate hosts (Baudrot et al., 2016). Therefore, the dynamics of *E. multilocularis* transmission might depend on the diversity of the prey community, encompassing both richness and relative abundance of species (Baudrot et al., 2016). Baudrot et al., 2016, developed a theoretical model for multi-host trophically transmitted parasites that fits the transmission of *E. multilocularis* and showed that a switch in the diet of the definitive host towards less-competent hosts driven by an increase in their relative density would decrease parasite transmission. The number of susceptible/competent intermediate hosts in a community of small mammals might also contribute to regulate the probability of definite host predation on a competent species and therefore parasite transmission. Mori et al., 2019, used a community analysis approach to assess *E. multilocularis* transmission in the North American city of Calgary and detected a higher prevalence of the parasite in definitive hosts when the community of small mammals had a higher proportion of susceptible species. This result suggests the existence of a dilution effect, whereby an increased diversity of species in host communities results in a decreased transmission (Civitello et al., 2015). This effect is supported also for definitive hosts by the continental-scale findings of Botero-Cañola et al., 2019, that modelled occurrence probability for *E. multilocularis* in North America using Maxent species distribution models. They found that definitive host species richness showed a negative relationship with *E. multilocularis* suitability and that the proportion of definitive hosts in the community of carnivores was positively related with *E. multilocularis* suitability (Botero-Cañola et al., 2019). Finally, the feeding behaviour of definitive hosts might mediate the effect of their density on parasite transmission, as a reduction of feeding on non-competent hosts when alternative resources are available might explain why in some instances the density of definitive hosts is negatively related to parasite transmission (Celva et al., 2023).

4.6. Intermediate hosts distribution

As the transmission of *E. multilocularis* occurs where there is an overlap between infected rodents and definitive hosts, and definitive hosts are typically widespread and with extremely large ranges (e.g., red fox, coyote), the distribution of intermediate hosts is more likely to constrain parasite distribution (Fig. 2; Guislain et al., 2007). Fuglei et al., 2008 and Stien et al., 2010, demonstrated that the intensity of *E. multilocularis* infection in arctic foxes (*Vulpes lagopus*) on the Spitsbergen island, Svalbard, was higher in the restricted area of the island where the density of the only intermediate host (*Microtus levis*) was higher. Guerra et al., 2014, investigated the relationship between the spatial occurrence of *E. multilocularis* in red foxes and the distribution of seven vole species in Ticino, Switzerland. The parasite was detected exclusively in the northern part of the studied region, and no expansion was registered throughout the 22 study years. The distribution of the parasite coincided with the distribution of *Microtus arvalis*, but not or only to a minor extent with the distribution of other voles, suggesting that the distribution of this key intermediate host limited the distribution of *E. multilocularis*. In a simulation experiment, Mori et al., 2023, provided support for the hypothesis that the distribution of intermediate hosts was among the main causes of the spatial heterogeneity of *E. multilocularis* infection in coyotes of Calgary, Canada.

Therefore, it seems likely that the distribution of intermediate hosts contributes to explain the distribution and infection patterns of *E. multilocularis* over different spatial scale, from local to the scale of continental range margins. However, the distribution of intermediate hosts alone cannot explain the distribution of *E. multilocularis* per se, but other factors should be considered as climate and alternative food sources can and do alter *E. multilocularis* survival and transmission (Raoul et al., 2015; Massolo et al., 2022).

4.7. Spatial scales

The spatial patterns of *E. multilocularis* infection result from a variety of factors acting at different scales. On a continental scale, definitive host dispersal, climatic conditions and host communities contribute to determine range boundaries. The same factors operate on smaller spatial scales up to the local scale, and their relative contribution depends on the spatial location, so that the relative importance of climate or land cover parameters might vary among e.g., different countries (Tolnai et al., 2013). On the local scale, the functional responses of carnivores to changes in intermediate hosts relative densities impact transmission and their defecation and marking behaviour interacts with the fine-scale habitat preferences of intermediate hosts to determine local transmission foci, e.g., in kitchen gardens or urban peripheries (Bastien et al., 2018). Future spatial models of *E. multilocularis* suitability and transmission should therefore consider the spatial scale and incorporate the relevant predictors accordingly. For example, definitive host mobility and dispersal patterns should be considered when predicting the future range of *E. multilocularis* and biotic variables should be increasingly considered in all modelling exercises, either directly or via land cover proxies that describe different communities of intermediate hosts (Mori et al., 2023). Models to predict the competence or susceptibility of different intermediate host species and experimental tests of rodent infection (as done by Woolsey et al., 2016) should also be done given the relevance of these species for *E. multilocularis* spatial transmission patterns.

5. Conclusions and perspectives

We provided an overview of the drivers of *E. multilocularis* transmission in wild hosts over multiple spatial scales. Future studies might aim to disentangle the relationships between transmission in wild and in domestic hosts, providing further insights on the spatial patterns of disease emergence in humans. Understanding the proximate drivers of a parasite distribution allows to build component-based species distribution models (i.e., models that account for host distribution and all factors directly affecting the life cycle and transmission of the parasite), that are more reliable than simple black-box algorithm relating parasite occurrence in definitive hosts with standard abiotic variables (Johnson et al., 2019). Our synthesis will therefore help to define the conceptual framework and the critical steps required to develop spatial predictive models of *E. multilocularis* distribution over the full spectrum of spatial scales. Higher-quality predictions of habitat suitability will in turn help to guide pre-emptive surveillance efforts for this relevant zoonotic parasite.

Open research statement

No data were collected for this study, besides those contained in the tables in the main document.

Declaration of Competing Interest

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

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