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One Health and sex and gender-related perspective in the ecosystem: Interactions among drivers involved in the risk of leptospirosis in Europe. A scoping review

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ABSTRACT

Leptospirosis has a complex transmission, involving rodents and many species of domestic and wild animals. Carrier animals spread leptospires, contaminating soil and water, the main sources of human infection. The risk of infection is modulated by socio-economic factors, environment and host animals and has changed, historically linked to agriculture but now prevalent in recreational environments. Leptospirosis also reveal gender-specific exposure patterns that determine infection risks. Emphasizing the interconnectedness of humans, animals, and the environment, the One Health approach highlights the ecosystem dynamics through which leptospires interact with hosts and abiotic factors, ensuring their survival and transmission.

We advocate for integrating gender considerations into the ecosystem dynamics of complex zoonoses, such as leptospirosis, through a One Health perspective. This approach, yet to be fully explored, may enhance our understanding of the infection and its modulating factors. A scoping review of the literature was conducted across Embase and Pubmed databases to collect information on sex and gender-specific drivers, sources of infections, environmental drivers, and related risks of leptospirosis. Quantitative data were extracted from the articles selected according to a list of criteria, and analyzed to discern sex and gender disparities and identify primary drivers of leptospirosis. We confirmed that the excess of male leptospirosis cases described in many parts of the world is also present in Europe. Furthermore, we identified environmental and sociocultural drivers and hypothesized their interactions between and within human, animal, and environmental sectors. These interactions modulate direct and indirect exposure to *Leptospira*, heightening infection risks across the ecosystem. Based on our findings, utilizing leptospirosis as a model, we advocate for integrating One Health and gender approaches in public health practices to better plan and implement more effective and timely intervention measures.

1. Introduction

Leptospirosis, a zoonotic illness caused by Leptospira bacteria residing primarily in the kidneys of several animal hosts, presents a complex transmission pattern. While small rodents like rats and mice serve as significant maintenance hosts for some *Leptospira* serovars, livestock and domestic animals also contribute to the maintenance of specific serovars. Infected animals may exhibit symptoms, yet carrier animals can asymptomatically shed leptospires over their lifetime, contaminating soil and water [1,2]. The long-term survival of Leptospires in the environment provides an important source of infection, in fact is usually through indirect contact with contaminated water and soil that people become infected, particularly when personal protective equipment (goggles, boots, gloves…) and protective behaviours, such as cover the wounds and abrasions, are not taken [1].

According to the European Centre for Disease Prevention (ECDC), leptospirosis notification rate in the period 2017–2021 in Europe was 0.20 confirmed cases per 100,000 population, with some fluctuations across years and countries. Cases were mainly males 45–64 years of age, and the male-to-female ratio was 3.6:1 [3]. Studies where disaggregated data were presented usually confirmed an excess in male cases [4–6].

Leptospirosis is a paradigmatic example of a complex disease influenced by multiple transmission routes, reservoirs, and risk factors. Socio-economic factors, environmental conditions, and several animal

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reservoirs influence the disease's dynamics, which was historically associated with agricultural exposure and now poses risks through recreational and residential activities [1,2,7].

Such complex dynamics impact the individual risk of infection, and social and behavioural factors modulate average exposure prevalence for *Leptospira*, producing a significant sex and gender bias [8].

Gender, as defined by the World Health Organization (WHO), encompassing social roles and behaviours learned and adopted differently by men and women, interacts with biological sex to influence health outcomes [9].

In addressing the complexity of leptospirosis, the holistic "One Health" approach emphasizes the interconnectedness of humans, animals, and environment in the ecosystem. The ecosystem encompasses a close functional interconnection between abiotic and biotic elements, as defined by Weißhuhn et al. [10]. This interconnectedness underscores the interdependence of organismal health within ecosystems, as posited by van Bruggen et al. [11].

Leptospires have complex interactions within the ecosystem in which they live, both with the different animal species that act as reservoirs/hosts for the pathogen, and with the abiotic component (water and soil), ensuring their long-term survival and viability and maintaining the transmission cycle [1,2]. Consequently, human exposure and the resulting risk of infection can be interpreted as one of the possible interconnections in the ecosystem, which are also modulated by social and cultural aspects related to gender.

Integrated One Health approach has garnered attention worldwide as a means to enhance the comprehension of leptospirosis, with specific emphasis placed on global [12], African [13], Brazilian [14], and Australian [15] contexts. This approach, which advocates for a holistic understanding of disease dynamics by integrating insights from human and animal health sectors, has undoubtedly advanced the understanding of leptospirosis epidemiology. However, despite recognizing environmental drivers as crucial elements in disease transmission, their analysis within integrated frameworks has often been inadequate.

Integrating gender considerations into One Health research facilitates a comprehensive understanding of risks at the human-animal-environment interface [16,17].

Despite their significance, gender considerations remain overlooked within the One Health framework and few studies have described the dynamic interactions among humans, animals and environmental factors with an ecosystemic vision.

This study would provide information about the different drivers of leptospirosis and their interaction to explain the different risks of infection by sex and gender in Europe from a One Health perspective.

2. Methods

We performed a scoping review of the literature to collect information on the sex and gender-specific drivers, sources of infections, environmental drivers, and the risk of leptospirosis. This approach has been standardized to ensure the quality and repeatability of the process following the reference provided by Tricco A. et al. on how to extend the PRISMA approach to scoping reviews protocol [18]. A predefined search strategy was developed and launched across Embase and Pubmed databases.

Studies with information on leptospirosis and sex/age and gender-specific variables, sources of infection, and environmental drivers were included. Research studies (i.e., studies generating new data) and data collections with abstract and full-text available in English, published after January 1st, 2001 were included. Studies without data or with duplicated data, patents, editorials, letters, and modelling studies with no data were excluded. Studies without a denominator or a reference population, or unavailable in full-texts, and those that referred to data older than 2000 or gathered outside Europe, including the United Kingdom were also excluded. One thousand and forty-five articles were retrieved after removing duplicates. For details on the search strategies, see supplementary material.

2.1. Study selection process and data extraction

The articles were uploaded to the Rayyan platform for systematic reviews [19]. Screening and labelling by three reviewers independently, according to the inclusion/exclusion criteria and the main topics of interest (sex/age, gender-specific drivers, sources of infection and environmental drivers), was conducted. The selection was conducted in two steps: reading titles and abstracts and, for those retained after the first step, the full texts. Details about the study selection process are shown in Fig. 1. Thirteen out of the 95 included articles were eligible for data extraction [6,20–31].

Data on sex/age, professions, recreational activities, specific behaviours, sources of infections, environmental drivers, and disease occurrence and incidence were entered in an Excel worksheet.

2.2. Data synthesis and statistical analysis

The male/female ratio of the leptospirosis cases was calculated from the extracted data and included in a random-effects meta-analysis was then performed to estimate the overall male/female ratio for leptospirosis in Europe. Age, as a continuous variable (median age of the cases) or categorical (age classes) and risk factors extracted as well, were included in metanalysis regression models to identify the interaction with the male/female ratio.

The descriptive statistics, metanalysis and multivariate analyses were carried out with Stata version 16.1 (StataCorp, 4905 Lakeway Drive College Station, Texas 77,845 USA).

3. Results

3.1. Characteristics of selected studies

The selected studies were conducted in Europe and were distributed in the five sub-regions: Eastern, Western, Southern, and Northern Europe. In particular, 3 were conducted in Croatia, 2 in France, 2 in Germany, 2 in Bulgaria, 1 in Ireland, 1 in Italy, 1 in Belgium, and 1 in Austria. All but one were research articles (12/13) that showed data and descriptions of gender-specific drivers, environmental drivers, and sources of infections. The study conducted in Austria was a review article. One out of the 13 articles showed data only for sex differences, environmental drivers, and sources of infections, and no gender-specific drivers were described. All studies were published between 2002 and 2018 (Table 1).

3.2. Sex and age distribution

The average male/female ratio among cases was calculated from 12 out of 13 studies. From the meta-analysis (Fig. 2), the estimated male/female ratio was 4.96 (95% CI = 2.94–6.98). The heterogeneity was estimated using the I^2 statistic, which describes the percentage of variation across studies due to heterogeneity rather than chance. The result of the I^2 statistic was 99.99%, meaning high heterogeneity. The two Bulgarian studies reported a % of male cases >90% [21,27]. Most of the cases were over 30 years old. However, some studies reported older (over 50 years) and younger cases (<30 years), the latter being exposed during leisure or sports activities [22]. The age predictor, included as median or age class in meta-regression models, was not significantly associated with the male/female ratio.

3.3. Drivers involved and their roles on risk of infection in the ecosystem

Table 2 and Fig. 3 list the leptospirosis discussed in the selected articles, providing a quantitative estimate of their importance through the frequency of extractions. Fig. 3 details the contributions of the single

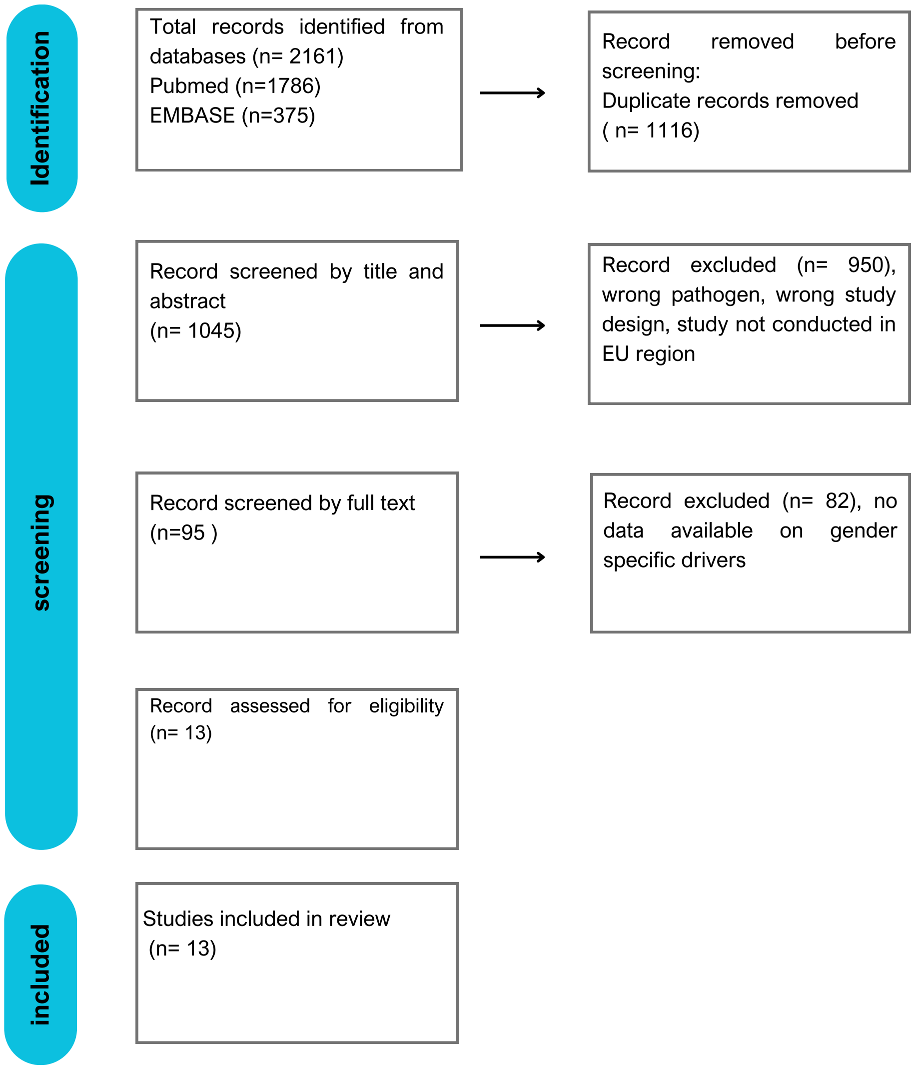

Fig. 1. PRISMA statement flow diagram.

drivers within the hierarchical categories. Fig. 4 shows the intra and interspecific relations among drivers involved in risk of infection of leptospirosis in the ecosystem.

Regarding gender drivers, eight studies out of the 13 showed recreational activities, particularly water sports, mentioned in 6 out of the 8 articles, related to the risk of infection. Seven studies out of the 13 mentioned occupations indicated farming as the activity at higher risk. Five studies out of the 13 reported risky behaviours, particularly having skin wounds not protected (three studies out of the five).

Regarding the environmental drivers, seasonality, reported as the number of cases of leptospirosis per month, was analyzed in 11 studies out of the 13, and 54% indicated the highest number of cases in August. Four studies measured the mean temperature before the outbreak took place; two of them considered the average daily temperature, which was 18.2–23.1 °C; in the third one, the average monthly temperature was measured, and it was very similar to the previous studies (15.3–25.2 °C); in the last, the average annual temperature was considered, resulting in lower values (11–13 °C). One study out of the 4 showed a specific range of bacterium survival temperature from 20 to 30 °C. Three studies out of the 13 showed an average daily precipitation range of 10.5–148 mm and an average annual precipitation range of 42.5–105.5 mm related to leptospirosis cases.

The role of wild and domestic animals as drivers of leptospirosis resulted in different animal species described as the source of human infection, in particular rodents, which were mentioned in six studies as direct or indirect sources of infection. Domestic animals, mainly pigs but also dogs and cattle, were reported in five studies, often associated with professional exposure (farmers). In one study, other wild animals (hares, wild boars and foxes) were reported as reservoirs of Leptospira and potential indirect sources of infection for humans. Animals are also reported as a source of environmental contamination, especially water and soil. Water was the identified source of infection in eight studies out of the 13; contaminated freshwater was mentioned in 6 of the 8 studies. Human infection due to contaminated soil was described in two studies out of the 13; in one, the infection was due to direct contact via flooded soil, and in the other one, to indirect contact with soil contaminated by animal urine and excrement. Two studies out of the 13 described infection via contaminated food, but the type of food remained unknown.

4. Discussion and conclusion

Our review summarizes the currently available evidence of leptospirosis drivers in Europe, providing a sex and gender focus within the One Health approach to the disease. We confirmed that an excess of male leptospirosis cases described in many parts of the world is also present in Europe, and this can be justified by occupational/recreational exposures and risky behaviours associated with the male gender [32].

Table 1
Data extraction table. Main drivers and sources of infection involved from 13 selected articles out 95 included.

First Author	Year of Publication	Article type	Geographic location	Gender driver	Environmental driver	Source of infection
Perra A	2002	research article	France	Risky Behaviours in recreational activities	Seasonality	Direct contact via contaminated water or indirect via excretings in water by seropositive rodents
Guillois Y	2018	research article		Risky Behaviours in Recreational activities	Seasonality	Direct contact via wild animals
Christova I	2003	research article	Bulgaria	Recreational and Professional activities at risk	Seasonality	Direct contact via domestic and rodents species or indirect via excretings in water, soil or food Direct contact via natural water deposits
Boland M	2004	research article	Ireland	Risky Behaviours in recreational activities	Seasonality	Direct contact via fresh water
Conti E	2005	research article	Italy	Recreational, Professional activities at risk	Seasonality	Direct contact via contaminated freshwater and via animals or animal urine
Desai S	2009	research article	Germany	Risky Behaviours in professional activities at risk	Seasonality Temperature/ Rainfall	Direct contact via contaminated soil or accidental contact via rodents
Brockmann S	2010	research article		Risky Behaviours in recreational activities	Seasonality Temperature/ Rainfall	Direct contact via contaminated freshwater
Tasseva E	2012	research article	Bulgaria	Recreational and Professional activities at risk	Seasonality	Direct contact via domestic and rodents species or via water, sewage or food
Mori M	2015	research article	Belgium	Recreational activities at risk	Seasonality	Direct/indirect contact via rodents
**Richard S*	2015	review article	Austria	Professional activity at risk	Temperature	Direct contact via wild animals
Topic MB	2009	research article	Croatia	Professional activities at risk	Seasonality (flooding), land use (rural areas)	Direct contact via contaminated well water
Misic-Majerus L	2017	research article		Professional activity at risk	Seasonality	Direct contact via water and domestic animals and rodents
Habus J	2017	research article		ND**	Temperature/Rainfall	Direct contact via domestic species

* No disaggregated data available for sex differences.
** Data available only for sex differences, none gender specific driver was described.

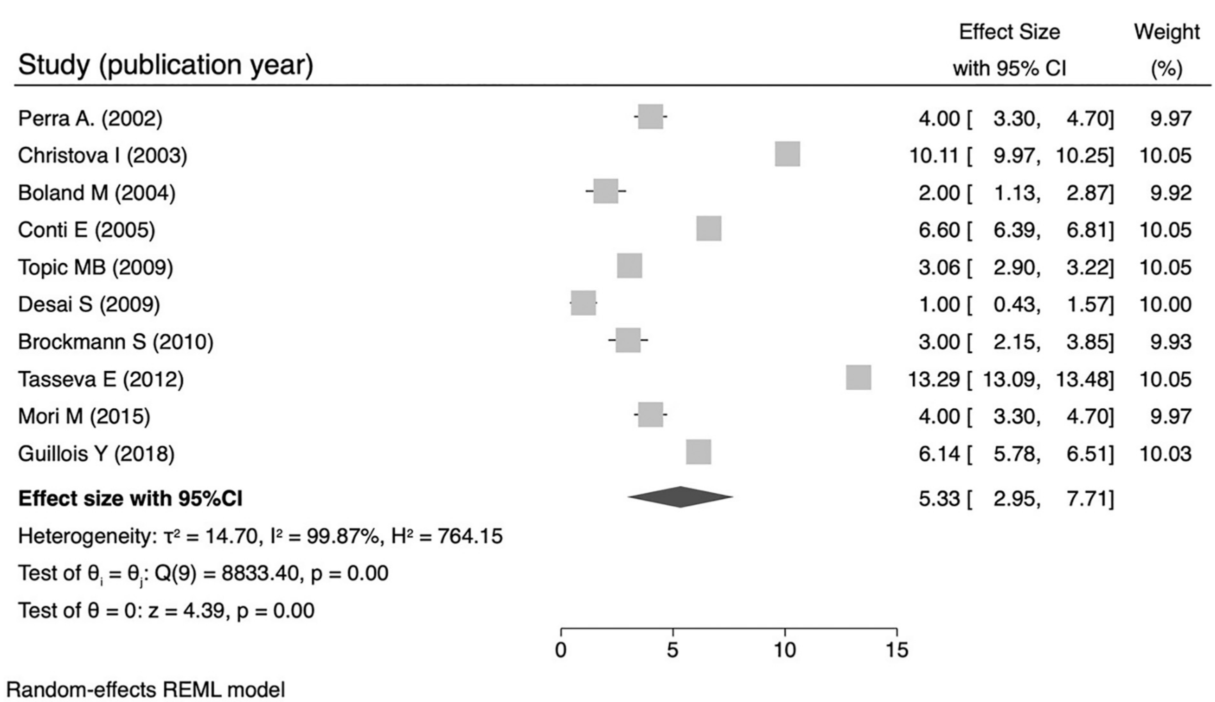

Fig. 2. Forest plot for the male/female ratio meta-analysis. Overview of all studies included in the meta-analysis. The grey squares indicate the effect size of each study, and the bars indicate a 95% confidence interval. The studies corresponding to the effect size are reported on the left and in Table 1. The black diamond at the bottom indicates the meta-analytic effect size and variance.

According to the proposed One Health and ecosystem approach, our study reveals that interactions within and between sectors (human, animal, and environmental) influence exposure to *Leptospira*, heightening infection risks across the ecosystem (Fig. 4). This aligns with the principle of 'one ecosystem, one health'. [10,11]. In the human sector, some activities and demographic factors, such as age and gender,

Table 2
Detailed drivers and sources of infection in decreasing order of frequency in the 13 selected articles out 95.

Driver	Variable	Description in detail	*No of studies (%)
Environmental			
Seasonality (11 studies)	Distribution in months	August	6 (54)
		June–August	1 (9)
		June–October	1 (9)
		July	1 (9)
		May–June	1 (9)
		October	1 (9)
Temperature (4 studies)	Average daily temperature	18.2–23.1 °C	2 (50)
	Average montly temperature	15.3–25.2 °C	2 (50)
	Average annual temperature	11–13 °C	1 (25)
	Temperature range (bacterium survival)	20–30 °C	1 (25)
Rainfall (3 studies)	Average daily precipitation	10.5–148 mm	2 (67)
	Average annual precipitation	42.5–105.5 mm	1 (33)
Sources of infection			
Animal (10 studies)	Infected species	Direct/indirect contact via rodents	6 (60)
		Direct/indirect contact via domestic species(swine, pigs, cattle, sheeps and goats, dogs)	5 (50)[§]
		Direct/indirect contact via wild species	2 (20)
Water (8 studies)	Kind of contaminated water	Contaminated fresh water	6 (75)
		Contaminated natural water deposits	1 (12)
		Contaminated well water	1 (12)
Soil (2 studies)	Kind of contaminated soil	Direct contact via flooded soil	1 (50)
		Indirect contact via excretings in soil	1 (50)
Food (2 studies)	Kind o contaminated food	Contaminated food (not specified)	2 (100)
Gender			
Recreational activities (8 studies)	Kind of outdoors activities	Water sports (kayaking, swimming, canoeing, triathlon and scouting)	6 (75)
		Recreational fishing	2 (25)
Professional activities (7 studies)	Kind of occupational activities	Livestock farming	3 (43)
		Agricolture	2 (29)
		Strawberry picking	1 (14)
		Forestry	1 (14)
Risky behaviours (5 studies)	Kind of risky behaviour	Having wounds without protections	3 (60)
		Swallowing small amount of water	1 (20)
		Eating unwashed strawberries	1 (20)

* One study may contain more drivers and descriptions.
§ Three studies out of 5 reported both domestic animals and rodents, are also included in the rodents group.

interact in ways that impact exposure. For instance, engaging in water sports like kayaking and triathlon (which includes swimming and is often practiced in lakes), raises the likelihood of exposure to *Leptospira*-contaminated water, particularly among young males prone to risky behaviours like inadequate wound care [30,33].

In the environmental sector, only one-way relationships among factors were observed. Seasonal changes influence climatic conditions, such as temperature and rainfall, which, in turn, affect water, soil, and food contamination. In particular, in areas where extreme weather events like floods occur, the spread and survival of *Leptospira* are increased, turning these environments into sources of infection [24–26,28,34].

The intricate interactions among rodents and other wild and domestic animals, which can serve as hosts or reservoirs for leptospires, impact the circulation and abundance of the pathogen within the ecosystem. The animal species' infection rates are influenced by intra-species and inter-species transmission among animals sharing the same habitat [6,21,27,35]. Furthermore, the dynamics of infection, guided by factors within sectors, shape the relationships among all sectors and influence the degree of *Leptospira* exposure in humans and animals, directly and indirectly. The mutual interaction between the human and animal sectors mediates exposure to excretions from infected wild and domestic animals.

In the interaction between humans and the environment, a two-way exchange facilitates exposure through contact with contaminated water, soil, and food. Similarly, bidirectional interaction occurs between the environment and animals, enabling direct exposure through contact with the aforementioned contaminated environmental matrices, facilitated by *Leptospira* excretions from reservoir species. From a sex and gender perspective, the described ecosystem interactions support the hypothesis that leptospirosis cases and outbreaks in Europe are often associated with recreational activities such as water sports. This hypothesis could explain the seasonal peak of cases during summer, a time conducive to these activities, as well as the demographic profile of cases, predominantly young men. It is conceivable that men in these age groups are more likely to engage in water sports than women. Additionally, the propensity of males to inadequately protect superficial wounds, coupled with their participation in water sports, increases the infection risk within this specific population.

In terms of environmental conditions, the risk of infection is influenced by specific factors. Studies indicate that the daily and annual temperature ranges are conducive to the survival of Leptospira, a finding supported by Fontaine et al., who demonstrated that *Leptospira* survival is temperature-dependent [36]. Moreover, the temperature in the optimal range for *Leptospira* survival (from 20 to 35 °C) favours the selection of pathogenic leptospires [37].

We confirmed the role of heavy rainfall in the increased transmission of leptospirosis [12,38,39]. The association of leptospirosis with rainfall and extreme weather events is well established, and those extreme weather events could force the interaction between infected species/reservoirs and humans while moving from hostile habitats to more suitable ones [12,38,39]. Such heavy rainfalls and associated floods are becoming more frequent due to climate change, which can affect the intensity and frequency of precipitation [40].

Barragan et al. suggested that animal reservoirs of *Leptospira*, like rats, and other animal species and humans, in case of flooding, may be forced to congregate in the same non-flooded places, increasing the likelihood of contact, allowing the infection to spread from the infected animals to non-infected ones and humans [41]. Contaminated freshwater was the more frequent source of infection among the environmental matrices mentioned in the selected studies. The release of urine by infected reservoir species ensures the presence of *Leptospira* in the environment, and its aggregation behaviour maintains effective bacterial concentrations even in large water bodies such as rivers and lakes, as suggested by Trueba et al. [42]. These factors help to explain why recreational water sports, usually practiced in these locations, are major risk factors for human leptospirosis in Europe.

As a limitation of this study, the drivers causing high leptospirosis rates in disadvantaged communities, particularly in urban and peri-urban settings, were poorly captured. In these settings, many of the animal and environmental drivers described in this study interact with socioeconomic drivers such as low socioeconomic status, inadequate sanitation infrastructure, and lack of safe drinking water enforcement to modulate the risk of infection [1]. This bias is probably due to the literature search criteria focused on Europe and quantitative studies, and suggests the need to investigate further into such settings.

In summary, the findings of this study suggest that:

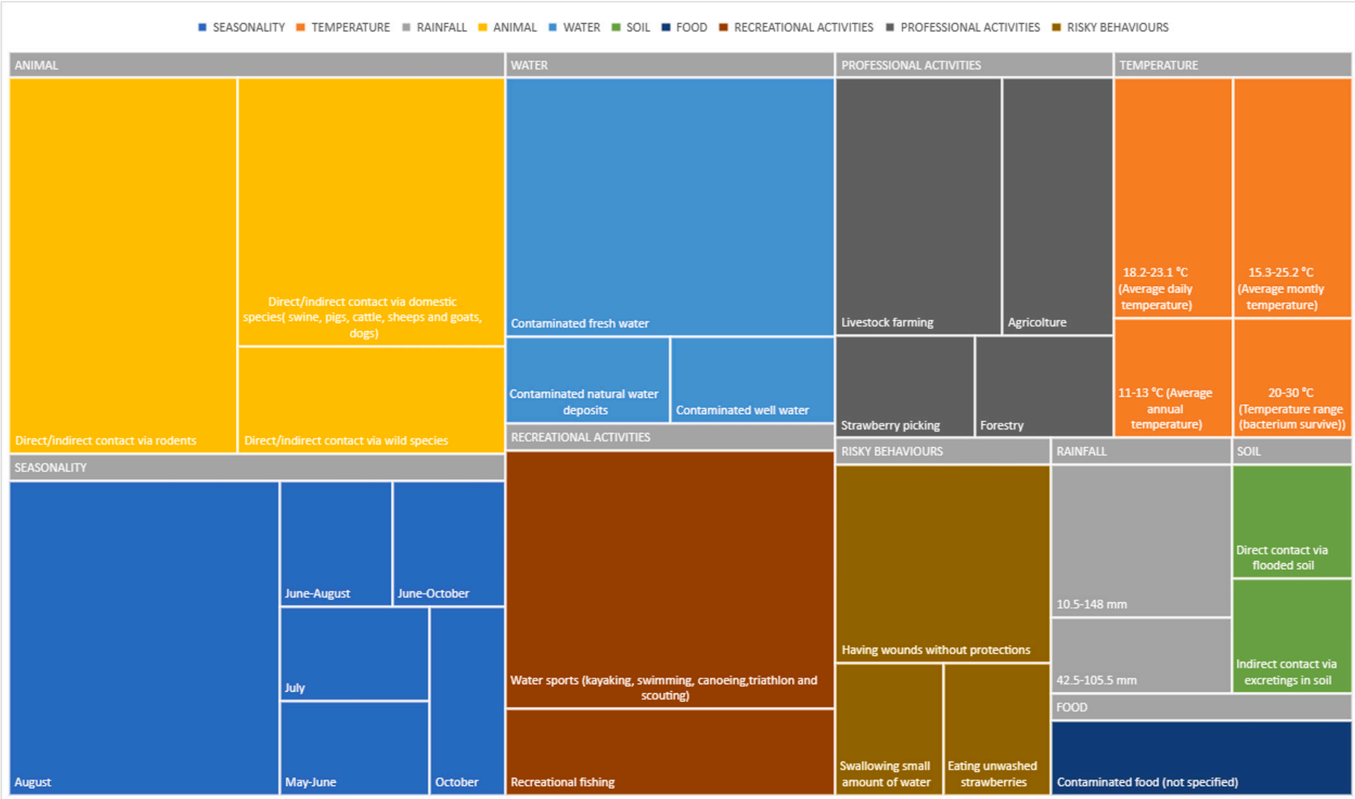

Fig. 3. Hierarchical representation of drivers. The size of the squares is proportional to the frequency of the driver extractions from the selected articles.

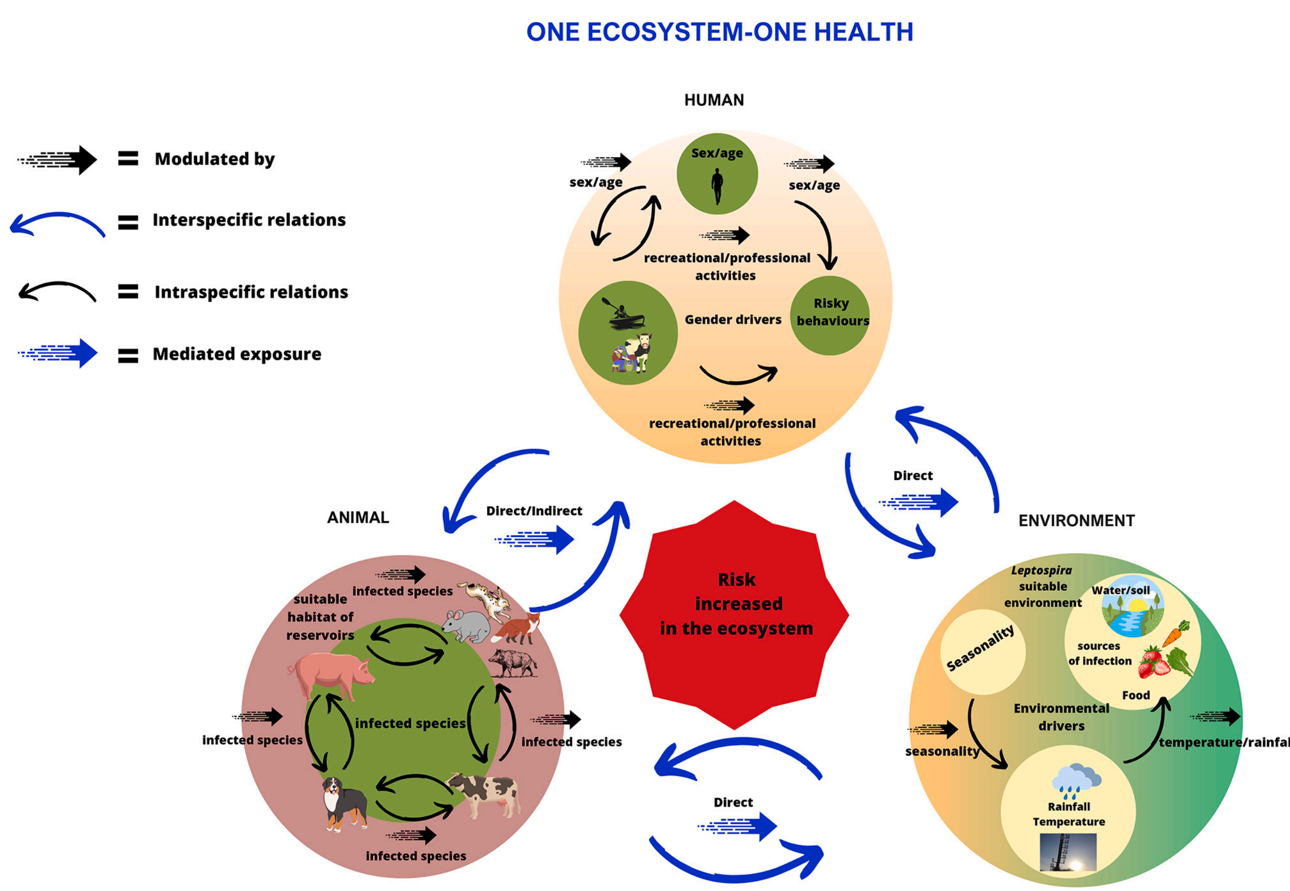

Fig. 4. One health visualization of intra and interspecific relations among drivers involved in risk of infection of leptospirosis in the ecosystem.

- specific populations engaging in risky behaviours are influenced by gender-based factors.
- infection rates among animal species, along with favourable climatic conditions and characteristics of the pathogen, contribute to the persistence of leptospires in the environment.
- Complex interactions among the sectors shape the risk of leptospirosis in the ecosystem.

Embracing a combined One Health and gender approach can enhance our ability to analyze, prevent, and mitigate risks at the human-animal-environment interface more effectively, identifying target groups and influencing factors [43–45]. Gender dynamics play a crucial role in the risk of infection for many zoonoses, including leptospirosis, due to asymmetric gender roles prevalent in most societies. To promote health and equity, it is imperative to devise mechanisms to design and foster socio-ecological systems that holistically sustain animals, people, plants, and ecosystems [46,47].

As part of public health interventions, environmental surveillance and early warning systems can be activated during specific periods, considering the seasonality of recreational activities and the at-risk populations. Such activities could be intensified in areas affected by heavy weather phenomena, like heavy rainfalls and floods, and combined with recommendations to avoid risky behaviours for specific population groups selected by sex, age and involvement in specific recreational activities such as water sports.

In conclusion, although integrating One Health and gender-specific approaches into the public health agenda is challenging and often ignored, this study points out that taking One Health and gender into account could help in planning and releasing more effective and timely interventions to reduce the possible emergence or re-emergence of leptospirosis outbreaks.

CRediT authorship contribution statement

Claudia Cataldo: Methodology, Writing – review & editing, Writing – original draft, Conceptualization, Investigation, Formal analysis. **Maria Bellenghi:** Investigation. **Roberta Masella:** Writing – review & editing. **Luca Busani:** Formal analysis, Supervision, Writing – review & editing.

Declaration of competing interest

None.

Data availability

Data available and already published in the literature articles listed in the references section

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.onehlt.2024.100841.

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