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Environmental and Occupational Factors Associated with Leptospirosis: A Systematic Review

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ABSTRACT

Background: Leptospirosis is a neglected emerging zoonotic disease with a profound public health impact worldwide with higher burden of disease in resource-poor countries. The environmental and occupational exposures contribute to human and animal transmission, but the interaction was less explored. A deeper understanding of the critical environmental and occupational drivers in different contexts will provide useful information for disease control and prevention measures.
Objective: This review aimed to summarize the potential environmental and occupational risk factors associated with leptospirosis infection.
Methods: Four databases (Scopus, Web of Science, Ovid MEDLINE, EBSCOhost) were searched for articles published from 2012 to 2021. Eligible articles were assessed using a checklist for assessing the quality of the studies. The quality of the articles was assessed based on the laboratory diagnosis approach and statistical analysis method.
Results: A total of 32 studies were included in this systematic review. Water-related risk factors such as natural water as the primary water source (AOR 1.8–18.28), water-related recreational activities (AOR 2.36–10.45), flood exposure (AOR 1.54–6.04), contact with mud (AOR 1.57–4.58) and stagnant water (AOR 2.79–6.42) were associated with increased risk of leptospirosis. Infrastructural deficiencies such as un-plastered house walls and thatched houses presented a higher risk (AOR 2.71–5.17). Living in low-lying areas (AOR 1.58–3.74), on clay loam soil (OR 2.72), agricultural land (OR 2.09), and near rubber tree plantations (AOR 11.65) is associated with higher risk of leptospirosis. Contact with rats (AOR 1.4–3.5), livestock (AOR 1.3–10.4), and pigs (AOR 1.54–7.9) is associated with an increased risk of leptospirosis. Outdoor workers (AOR 1.95–3.95) and slaughterhouse workers (AOR 5.1–7.5) have higher risk of leptospirosis.
Conclusion: The environmental and occupational components related to water, infrastructure, landscape, agriculture, and exposed animals play an essential role in leptospirosis transmission. The magnitude of those risk factors differs with geographical region, climate factor, urbanization and population growth, and the country's socioeconomic status.

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1. Introduction

Leptospirosis is a neglected emerging zoonotic disease with a profound public health impact worldwide [1,2]. It is the most common bacterial zoonosis that is caused by spirochetes of the *Leptospira* genus. More than 200 serovars of *Leptospira* have been identified and the bacteria circulate in various hosts, including wild and domestic animals [3]. Leptospirosis has a wide geographical distribution, with morbidity and mortality being highest in countries with poor resources and areas where disease monitoring is not routinely performed [4]. The most recent estimates indicate that there are 1.03 million annual cases of leptospirosis, with 58,900 deaths worldwide [4]. This zoonotic disease causes life-threatening manifestations such as severe pulmonary hemorrhage syndrome, which has a case fatality rate of >50%, attributed to the major disease burden [5].

The estimated global burden of leptospirosis is 2.9 million disability-adjusted life years, which corresponds to the loss of 1 year of healthy life for the whole population of a city the size of Rome [6]. Furthermore, with men and young adults accounting for 80% and 52% of the total burden, this illness has a major economic impact, particularly in low- and middle-income nations where young adults constitute the most important demographic for economic output [6]. Leptospirosis incidence is expected to surge [7], as global demographic trends tend to shift due to urbanization, particularly in Asia and Africa [8]. Moreover, these two regions are also at risk of climate change and extreme weather events such as heavy rainfall, floods, droughts, and hot weather [9]. Studies reveal that climate change will likely increase the probability of leptospirosis emergence and outbreaks [10–12].

Humans acquire *Leptospira* through direct contact with various types of maintenance mammalian hosts or indirect exposure to surface water or soil in a contaminated environment, where the organism can survive for several weeks after excretion from chronic animal [3,13,14]. Heavy rain and flooding, high temperatures, animal exposure, inadequate sanitation, and improper waste disposal all impact leptospirosis epidemiology. Many of these major risk factors are expected to occur with greater frequency and intensity as a result of global climate change and urbanization, potentially leading to increased leptospirosis incidence and outbreak [7].

Certain occupational types are reported to be at high risk of contracting leptospirosis, as the occupation exposes them to contaminated water, soil, and animals. Workers involved in agriculture and animal husbandry, such as paddy field farming, handling livestock and slaughtering animals, and working at kennel; are those exposed to leptospiral in their working environment [15–18]. These are also possible risks for those who are involved in military training and on-duty assignments, outdoor water sports, and recreational activities, and the reported cases were usually related to skin injury [19–21].

The ecology of leptospirosis consists of the interaction between humans, animal reservoirs, leptospiral, and the environment in which they reside. Various environmental risk factors for infection may differ depending on the ecological settings [7,12,22]. Once the pathogens are shed and persist in the environment, entire populations could be at risk for leptospirosis. However, the risk of contracting the disease is higher in a person who works with animal and their products, which direct contamination from the animal excreta can occur. Besides, leptospirosis also can be transmitted indirectly from the mammalian host such as cattle to the farmers or workers in the pens through the environment. There is a particular need to assess the leptospirosis environmental and occupational components, plus their interactions to develop acceptable, feasible, and successful public health strategies to control or prevent this infectious disease. Thus, this review summarises the potential environmental and occupational risk factors associated with leptospirosis infection. A deeper understanding of the critical environmental and occupational drivers in different contexts will provide useful information for disease control and prevention measures.

2. Methods

This systematic review is registered with PROSPERO (CRD42022313362) and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [23].

2.1. Research question formulation

A review of risk type is aimed at determining the association between risk factors and health outcomes. In this systematic review of etiology/risk type, we used the PEO (P, population; E, exposure; O, Outcome) concept to guide the formulation of the review question [24]. Based on the PEO concept, population refers to the general population, the exposure of interest is an environmental and occupational risk factor, and the outcome is leptospirosis infection in humans. Therefore, the developed review question was 'What environmental and occupational factors are associated with leptospirosis in humans?'

2.2. Systematic searching strategies

Synonyms and variations were used in the identification stages to enrich the keywords, which were then used during the search process. The search string was created and generated using Boolean operators and keyword search, as shown in Table S1. A systematic literature search was performed on four primary databases: Scopus, Web of Science, Ovid MEDLINE, and EBSCOhost. All potential records were exported from the databases and arranged for title and abstract screening in an Excel sheet.

2.3. Inclusion and exclusion criteria

The inclusion criteria were: (1) publication within the ten years from 2012 to 2021; (2) full original article in a journal; (3) Englishlanguage article; (4) observational study design, including cohort, case-control, cross-sectional, and ecological studies. We excluded systematic review articles, conference proceedings, book chapters, and reports.

2.4. Study selection and eligibility criteria

Two researchers screened the titles and abstracts of the potential records independently based on the review question with the inclusion and exclusion criteria. Disagreements were resolved by discussion to reach a consensus.

2.5. Quality assessment

The quality of the studies was assessed based on the laboratory diagnosis approach and statistical analysis method. For laboratory diagnosis, we utilized the World Health Organization (WHO) standard laboratory diagnosis criteria [25] and the Centers for Disease Control and Prevention guidelines [26]. The quality assessment for laboratory diagnosis was divided into 3 groups as follows:

- Quality 1 - Studies that reported confirmed laboratory diagnosis of leptospirosis. The confirmed laboratory diagnosis was either:
  - o Isolation of *Leptospira* spp. by culture of clinical specimens
  - o Detection of pathogenic *Leptospira* DNA via PCR
  - o Demonstration of *Leptospira* by direct immunofluorescence
  - o *Leptospira* agglutination titer of ≥800 by microscopic agglutination test (MAT) for a single specimen or ≥4-fold increase in the titer for paired specimens.
- Quality 2 - Studies that reported leptospirosis cases using supporting laboratory criteria diagnosis as follows:
  - o *Leptospira* agglutination titer of ≥200 but <800 by MAT [26].
  - o Enzyme-linked immunosorbent assay (ELISA) detection of immunoglobulin IgM or IgG antibodies against *Leptospira* in serum specimens.
- Quality 3 - Studies that reported the study outcome as 'confirmed leptospirosis cases' without clarifying any laboratory approach for diagnosis.

2.6. The quality assessment for the statistical analysis method was divided into 3 groups as follows

- Quality 1 - Studies that used multivariable or multiple logistic regression as the method of analysis. The result comprised adjusted odd ratios, 95% confidence intervals (CIs), and statistical significance levels (p-values) for predictors.
- Quality 2 - Studies that used bivariate analysis such as the Chi-square test or Fisher's exact test.
- Quality 3 - Studies with CI and equivalent measures were not specified.

The average score of the two assessments (laboratory diagnosis approach and statistical analysis method) was taken as the final quality score.

2.7. Data extraction and synthesis

Two researchers extracted the data independently using a standardized data extraction form and organized it in a standard Microsoft Excel 2019 spreadsheet. The information collected included: (1) authors, (2) publication year, (3) country, (4) study location, (5) study design (cohort, case-control, cross-sectional, ecological time series), (6) study population (general population, hospital-based/patients, workers), (7) sample size, (8) sampling method (random sampling, cluster sampling, non-random sampling, or no description of sampling method), (9) statistical analysis method, (10) environmental factor-related findings, and (11) laboratory diagnosis methods.

The environmental risk factors associated with leptospirosis were classified into five categories and further divided into sub-categories as below:

- Water-related
  - o Natural water bodies as a source of water consumption
  - o Exposure to stagnant water
  - o Involvement in recreational water activities such as swimming or bathing
  - o Contact with mud
  - o Distance to the natural water body
  - o Rainfall patterns
  - o History of flood exposure
- Infrastructure
  - o Working in a cooler-shaded slaughterhouse
  - o Infrastructural deficiencies (un-plastered walls or thatched house)
  - o Near to garbage dumping area
  - o Poor sewerage system

- Landscape
  - o House in a low-lying area
  - o Proximity to a rubber tree plantation
  - o Residence in rural areas or villages or settlements
- Agricultural
  - o Working in wet cultivation
  - o Agricultural work

The animal exposure risk factors were classified into exposure to:

- Rats
- Poultry
- Livestock
- Pigs
- Cats and dogs
- Other animals such as deer and monkeys

For occupational exposure risk factors, it was further classified into:

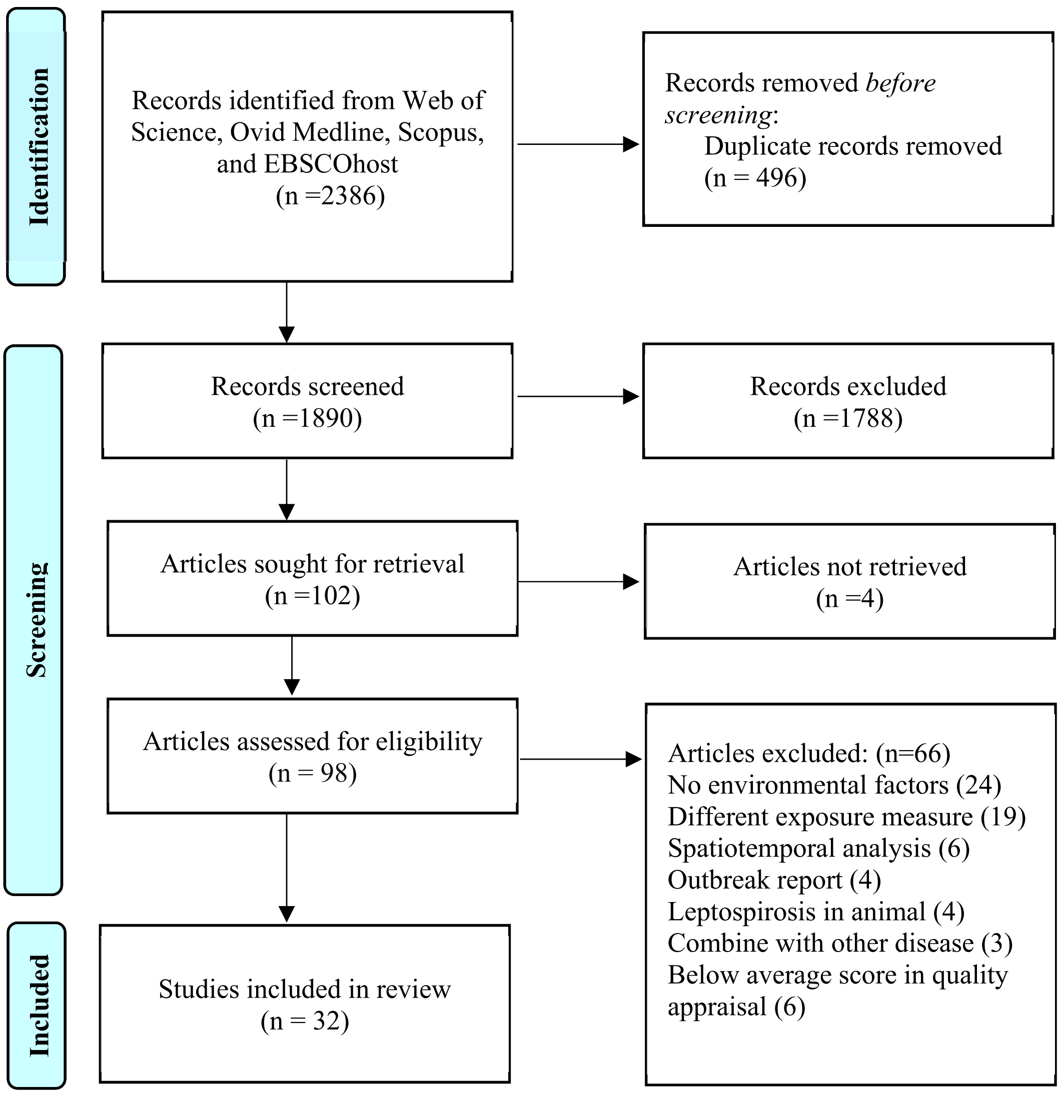

Fig. 1. PRISMA flow diagram.

Table 1
Summarises of environmental factors associated with leptospirosis cases.

Author, year, country	Water-related							Infrastructure				Landscapes			Agricultural	
	Used natural water body	Stagnant water	Recreational water activities	Contact with mud	Distance to a water body	Rainfalls	Flood	Cooler-shaded slaughterhouse	Infrastructural deficiencies (Type of house)	Garbage dumping area	Sewerage system	House in a low-lying area	Rubber tree plantation (proximity)	Rural/ villages/ settlement	Working in the wet cultivation	Agricultural works
Briskin et al., 2019, Puerto Rico					/		/									
Cook et al., 2017, Kenya	/							/								
Costa et al., 2014, Brazil		/							/							
Daud et al., 2018, Malaysia										/						
Desai et al., 2016, India			/						/		/					
Felzemburg et al., 2014, Brazil											/					
Hacker et al., 2020, Brazil						/										
Hegazy et al., 2021, Egypt				/												
Hinjoy et al., 2019, Thailand			/										/			
Kamath et al., 2014, India				/	/											
Lau and Clements et al., 2012, American Samoa				/								/				/
Lau et al., 2016, Republic of the Fiji Islands					/	/					/			/		

(*continued on next page*)

Table 1 (*continued*)

Author, year, country	Water-related							Infrastructure				Landscapes			Agricultural	
	Used natural water body	Stagnant water	Recreational water activities	Contact with mud	Distance to a water body	Rainfalls	Flood	Cooler-shaded slaughterhouse	Infrastructural deficiencies (Type of house)	Garbage dumping area	Sewerage system	House in a low-lying area	Rubber tree plantation (proximity)	Rural/ villages/ settlement	Working in the wet cultivation	Agricultural works
Matsushita et al., 2018, Philipines						/										
Maze et al., 2018, Tanzania															/	
Meny et al., 2019, Uruguay	/						/									
Narayanan et al., 2016, India		/							/							
Narrkkul et al., 2021, Thailand	/															
Prabhakaran et al., 2014, India					/										/	
Rafizah et al., 2013, Malaysia			/													
Raj et al., 2018, India	/		/						/			/		/		/
Ridzuan et al., 2016, Malaysia										/						
Sohail et al., 2018, Pakistan	/						/									
Total	5	2	4	3	4	3	3	1	4	2	3	2	1	2	2	2

- Urban
- Forestry
- Slaughterhouse
- Military
- Farmer
- Non-specific outdoor-type occupations
- Occupation related to animal and water-related

3. Results

3.1. Study identification, screening, and selection

Study identification, screening and selection are summarized in Fig. 1. Systematic searching identified a total of 2386 relevant records. We removed 496 duplicate records, leaving 1890 records for title screening. The screening process eliminated 1788 articles, leaving 102 for full-text retrieval for further assessment and eligibility screening. Despite our best efforts, we were unable to retrieve four reports from the databases or through a published article search [27–30]. Of the 98 remaining, after critical review of full text, sixty articles were excluded due to: (1) the absence of environmental factors (n = 24), (2) different exposure measurement (n = 19), (3) focus on spatiotemporal analysis (n = 6), (4) it being an outbreak report and case study (n = 4), (5) focus on leptospirosis in animals (n

Table 2
Type of animal's exposure associated with leptospirosis cases.

Author, year, country	Rat	Poultry	Livestock	Pig	Cat & dog	Others
Awosanya et al., 2013, Nigeria					OR 15.0 (95% CI 1.5–759)	
Brockman et al., 2016, Germenay	RR 13.9 (95% CI 4.80, 25.30)	RR 3.6 (95% CI 1.30, 8.60)	Cattle RR 3.7 (95% CI 1.30, 9.60), RR 2.3 (95% CI 1.10, 4.90)			Guinea pig RR 3.0 (95% CI 1.10, 7.40)
Costa et al., 2014, Brazil	AOR 2.80 (95% CI 1.06, 7.36)					
Desai et al., 2016, India	OR 2.95 (95% CI 1.20, 3.30)					
Dreyfus and Benschop et al., 2014, New Zealand			AOR 10.4 (95% CI 2.80, 38.80)			Deer AOR 12.7 (95% CI 1.33, 120.60)
Dreyfus et al., 2016, Uganda			AOR 12.3 (95% CI 1.40, 108.60)			Monkey AOR 1.92 (95% CI 1.20, 3.10)
Hagan et al., 2016, Brazil	AOR 1.46 (95% CI 1.00, 2.16)					
Hegazy et al., 2021, Egypt			AOR 8.0 (95% CI 1.55, 41.23)			
Kamath et al., 2014, India	AOR 3.5 (95% CI 1.30, 9.28)					
Lau and Dobson et al., 2012, American Samoa				AOR 2.66 (95% CI 1.55, 4.57)		
Lau and Clements et al., 2012, American Samoa				OR 1.15 (95% CI 1.05, 1.26)		
Lau et al., 2016, Republic of the Fiji Islands			AOR 1.04 (95% CI 1.02, 1.06)	AOR 1.54 (95% CI 1.21, 1.98)		
Maze et al., 2018, Tanzania	AOR 1.4 (95% CI 1.00, 2.10)					
Meny et al., 2019, Uruguay	OR 2.79 (95% CI 1.32, 5.91)					Animals OR 4.96 (95% CI 1.29, 19.07)
Narayanan et al., 2016, India	AOR 224.6 (95% CI 14.1, 1125.1)					
Prabhakaran et al., 2014, India	AOR 2.6 (95% CI 1.66, 4.08)		AOR 2.30 (95% CI 0.32, 16.54)			
Raj et al., 2018, India						Animals AOR 3.64 (95% CI 2.00, 6.63)
Ridzuan et al., 2016, Malaysia	AOR 3.27 (95% CI 1.72, 6.19)		AOR 4.78 (95% CI 2.76, 8.26)			
Sanhueza et al., 2015, New Zealand			AOR 4·6 (95% CI 1·30, 16·10)	AOR 7·9 (95% CI 1·70, 37·50)	AOR 9.2 (95% CI 1.40, 62.80)	

AOR, Adjusted odds ratio; OR, Odds ratio; RR, Relative risk; CI, Confidence interval.

= 4); or (6) the study outcomes being combined with other diseases (n = 3). Subsequently, the remaining 38 articles proceeded to quality appraisal. The quality appraisal score of eligible articles is presented in Table S2. Finally, a total of 32 articles (with an average score of ≤2) were included in this review.

3.2. Characteristics of eligible studies

The characteristics of eligible study are listed in Table S3. A total of 32 studies fulfilled the eligibility criteria and were included in this systematic review. Of the 32 studies, 14 (43.8%) were conducted in South and Southeast Asia, six (18.8%) were from Oceania, five

Table 3
Type of occupational exposure associated with leptospirosis cases.

Author, year, country	Urban worker	Forestry worker	Slaughterhouse workers	Military	Outdoor type occupation	Farmers	Related to animal and environmental water
Atil et al., 2020, Malaysia	Sweeper OR 2.29 (95% CI 1.13, 4.61)						
Brockman et al., 2016, Germany		RR 9.2 (95% CI 2.60, 21.40)					
Cook et al., 2017, Kenya			AOR 5.1 (95% CI 1.80, 15.00)				
Desai et al., 2016, India							Waterlogged fields OR 4.6 (95% CI 1.60, 17.90)
Dreyfus and Wilson et al., 2014, New Zealand			Removal of high-risk material (Bladder, and kidneys) RR 5.2 (95% CI 1.70, 16.00), Beginning of the slaughter line (yards, stunning, pelting) RR 7.5 (95% CI 2.50, 22.40) Offal/pet food area RR 4.1 (95% CI 1.00, 16.40)				
Dreyfus and Benschop 2014 et al., 2014, New Zealand			AOR 6.5 (95% CI 1.40, 29.80)				
Dreyfus et al., 2021, Bhutan				AOR 26.65 (95% CI 1.44, 494.28)			
Kamath et al., 2014, India					AOR 3.95 (95% CI 1.19, 13.0)		
Lau and Dobson et al., 2012, American Samoa					AOR 2.09 (95% CI 1.43, 5.06)		
Lau et al., 2016, Republic of the Fiji Islands					AOR 1.64 (95% CI 1.15, 2.34)		
Maze et al., 2018, Tanzania						AOR 1.6 (95% CI 1.00, 2.30)	
Narrkkul et al., 2021, Thailand							AOR 4.31 (95% CI 1.17, 15.83)
Prabhakaran et al., 2014, India	Building workers AOR 3.76 (95% CI 0.72, 19.70)						
Rafizah et al., 2013, Malaysia					AOR 1.95 (95% CI 1.22, 3.13)		

AOR, Adjusted odds ratio; OR, Odds ratio; RR, Relative risk; CI, Confidence interval.

each were from Africa (15.6%) and South America (15.6%), and one study each was from North America (Puerto Rico) and Europe (Germany). India was the country with the most eligible studies (n = 5), followed by Malaysia (n = 4), Brazil (n = 4), and New Zealand (n = 3). Most of the studies were performed in upper-middle-income countries (13/32, 40.6%) which are Brazil (n = 4), Malaysia (n = 4), Thailand (n = 2), American Samoa (n = 2) and the Republic of Fiji Islands (n = 1). Twelfth (12/32, 37.5%) studies were performed in lower-middle-income countries. The 12 studies include 5 studies from India, and one study each from Nigeria, Kenya, Bhutan, Egypt, Philippines, Tanzania, and Pakistan. Six studies were conducted in high-income countries which are Germany (1), New Zealand (3), Puerto Rico (1), and Uruguay (1). One eligible study was from a lower-income country, which is Uganda.

Most of the eligible studies were cross-sectional studies (20/32, 62.5%). Seven studies were case-control studies, and the remaining five were cohort (n = 4) and time series studies (n = 1). Regarding the study population, 23 studies (71.9%) involved the general population, eight studies (25%) involved workers, and one study (3.1%) was hospital-based, involving patients. Twenty-two (68.8%) studies used paired MAT for diagnosing leptospirosis. Eighteen studies (56.3%) were published between 2012 and 2016, and the remaining 14 were published between 2017 and 2021.

3.3. Water as an environmental risk factor for leptospirosis infection

Table 1 summarises the environmental risk factors related to water, infrastructure, landscape, and agriculture. The details on the odds ratio of environmental risk factors related to water, infrastructure, landscape, and agriculture are tabulated in Table S4. Water-related environmental risk factors were the most investigated risk factor in 26 studies (81.3%), with 18 studies (18/26, 69.2%) reporting a statistically significant result. In five studies [31–35], the source of water consumption and usage from the natural water body was associated with an increased risk of leptospirosis infection [odds ratio (OR) 1.8–18.28]. The highest OR (18.28) was from a cross-sectional study involving the general population in South Andaman Island, India [34]. In this study, people who used streams as a water source for washing were more likely to be infected [adjusted OR (AOR) 18.28]. The study also reported that using water from a pond (AOR 10.63) and public taps (AOR 2.84) for washing, and water from tube wells for drinking (AOR 3.12) was associated with leptospirosis seropositivity. Moreover, the study reported that having a private tap as a source of drinking water was a protective factor against leptospirosis infection (AOR 0.401) [34]. Another study that reported water-related environmental factors was conducted in Sisaket and Nakhon Si Thammarat, Thailand. People who consumed water from more than two natural body sources were found to have higher odds (AOR 10.74) of leptospirosis infection [33].

Water-related recreational activities such as swimming in canals (AOR 3.2) [36] and ponds (AOR 5.30) [34], bathing in natural water bodies (AOR 10.45) [37] and ponds (AOR 2.99) [34], and having a recent history of water-related recreational activities (AOR 2.36) [38] were associated with leptospirosis infection. Four studies reported that distance from the water body was a significant factor for leptospirosis infection (OR 1.43–3.88). The highest OR was reported by Kamath et al. [39], where the presence of drainage within a 15-m radius of a home presented higher odds for infection (AOR 3.88), followed by house location near water bodies (AOR of 3.87) [40] and the home being <100 m from a major river (AOR 1.41) [41]. Moreover, one study reported a protective factor, where increasing the household's distance from the canal by 10 m was associated with decreased risk of infection (AOR 0.934) [42].

The other water-related environmental risk factors were rainfall (AOR 1.53–13.77), flood exposure (AOR 1.54–6.04), contact with mud (AOR 1.57–4.58), and contact with stagnant water (AOR 2.79–6.42). A study from the Philippines reported that the risk of post-rainfall leptospirosis infection would increase as rainfall intensity increased. The reported relative risks (RRs) were as follows: light rainfall, RR 1.3; moderate rainfall, RR 1.53; heavy rainfall, RR 2.45; intense rainfall, RR 4.61; and torrential rainfall, RR 13.77 [43]. In contrast to the hospital-based study [44], there was an inverse association between *Leptospira* infection risk in urban areas with cumulative rainfall (AOR 0.986 per cm). Two studies reported a positive association between flood and *Leptospira* infection for flood exposure [32,35]. In contrast, a study conducted in Puerto Rico reported that household flooding was inversely associated with *Leptospira* infection risk (AOR 0.12) [42].

3.4. Infrastructure as an environmental risk factor for leptospirosis infection

Nine studies [15,31,34,36,41,45–48] reported infrastructure-related risk factors. The most frequent were infrastructure deficiencies (OR 2.71–5.17). Studies from India found that living in thatched houses and houses with mud walls presented higher infection risk (AOR 3.86 and 5.17, respectively) [34,47]. Another study conducted in India found that houses made from brick presented a lower infection risk (OR 0.6). Infrastructural deficiencies such as un-plastered walls in the house presented higher infection risk (AOR 2.71) [45]. Poor sanitation such as lack of treated water in the home (AOR 1.52) [41] and open-air defecation (OR 1.7) [36] were environmental risk factors for *Leptospira* infection. Two studies from northeast and south Malaysia reported that the presence of garbage dumping areas in a farm (AOR 2.4) [15] and the presence of a landfill in plantations (AOR 2.04) [48] presented a higher risk of *Leptospira* infection among cattle farmers and plantation workers. In Brazil, increasing the distance of a residence from an open sewer by 1 m was a significant protective risk factor against secondary *Leptospira* infection (AOR 0.95) [46]. Lastly, a study conducted among slaughterhouse workers in western Kenya found that a cooler-shade slaughterhouse with a roof had a higher risk of leptospirosis seropositivity (AOR 2.6) [31].

3.5. Landscape and agriculture as an environmental risk factor for leptospirosis infection

Landscape plays an essential role in leptospirosis transmission. Studies conducted in the Republic of the Fiji Islands and South Andaman Island found that living in rural areas (AOR 1.43 and 2.21, respectively) [34,41], settlements (AOR 2.13) [41], and villages

(AOR 1.64) [41] presented a higher risk of *Leptospira* infection. A house below the median altitude of the village (OR 1.58) [49] and in low-lying areas (AOR 3.74) [34] presented a higher risk of infection. Furthermore, living on clay loam soil (OR 2.72) [49], agricultural land (OR 2.09) [49], and near rubber tree plantations (AOR 11.65) [37] also increased infection risk. Three studies showed significant agricultural risk factors related to *Leptospira* infection. Recent fieldwork (AOR 14.743) [34], involvement in wet cultivation (AOR 4.59) [40], and work in rice fields (AOR 2.7) [50] presented higher infection risk.

3.6. *Animal exposure risk factors*

Table 2 shows a summary of the association between animal exposure type and leptospirosis cases. Rats play a significant role in *Leptospira* transmission, given that 10 out of 11 studies that investigated exposure to rats reported statistically significant findings (OR 1.4–224.6). Eleven studies evaluated exposure to rats, but the definition of exposure varied broadly, such as rat infestation, seeing rats around the house, or physical contact with rats. Most of the studies were performed in Asia (n = 5) and South America (n = 3). The highest OR was from a study conducted in Chennai, India, which focused on pediatric leptospirosis with a relatively small number of confirmed leptospirosis cases (n = 35) as the sample. Therefore, the 95% CIs were wide (14.1–1125.1) [33]. Other studies showed relatively similar ORs of 1.4–3.5, except the study by Brockmann et al. [51] from Germany, where there were slightly higher RRs of seropositivity due to contact with pet rats (RR 13.9) and guinea pigs (RR 3.0). Two studies that evaluated exposure to rats reported statistically significant findings in univariate analysis; however, they were not significant in the multivariate model [40,48].

Livestock (8 studies), pig (3 studies), and poultry (1 study) production were associated with increased infection risk. Direct contact with livestock [51–55] and pigs [55] increased infection risk. For livestock, the OR was 1.04–12.3. The highest OR was reported in a study conducted in Uganda among adults visiting the Kikuube and Kigorobya Health Centers. Skinning cattle was a high-risk activity with higher odds (12.3) for *Leptospira* seropositivity compared with non-cattle skinning activity [53]. The second highest livestock-related infection risk was reported in a study conducted in New Zealand among abattoir workers. In sheep abattoirs, workers at the beginning of the slaughter floor who are involved in stunning and pelting had higher odds (10.4) than those working in the middle or end of the slaughter floor who perform tasks such as gut removal and pulling kidneys in the offal room [52]. Other than that, the presence of livestock and piggeries around the house also increase the likelihood of infection (OR 1.04–4.78 and 1.15–2.66 respectively) [40,41,48,49,56].

3.7. *Occupational exposure risk factors*

Table 3 summarises the occupational exposure associated with leptospirosis cases. The occupation was an important risk factor for leptospirosis infection. Occupational exposure was the second most frequently investigated factor, i.e. in 23 studies (71.9%). Of the 23 studies, 18 (78.3%) reported statistically significant results. Working in the slaughterhouse presented the highest infection risk (OR 5.1–7.5). The highest OR was from a study conducted in New Zealand among meat workers. Different work positions and tasks in the

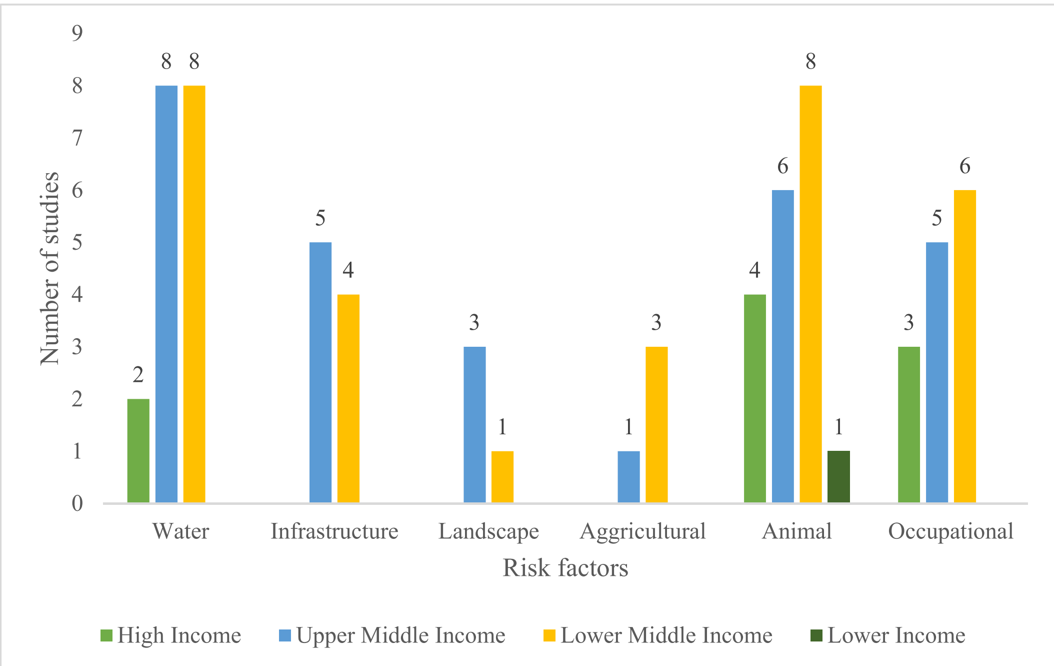

Fig. 2. Risk factors associated with leptospirosis stratified by countries' economies.

slaughterhouse yielded different risk measures. New *Leptospira* infection risk was highest at the beginning of the slaughter line (RR 7.5) and lower at the middle and end of slaughter line production [57]. Outdoor occupations presented a higher infection risk (OR 1.64–3.95). Forestry workers (AOR 9.2) [51], military (AOR 26.65) [58], urban sweepers (OR 2.29) [59], construction workers (AOR 3.76) [40], and farmers (AOR 1.6) [50] also had a higher risk of *Leptospira* infection.

3.8. Risk factors stratified by economic classification and climatic zone

Fig. 2 shows the risk factors associated with leptospirosis infection stratified by countries' economic classification. Water-related risk factors were frequently significant in studies conducted in upper and lower-middle-income countries. In studies conducted in high-income countries, animal and occupational exposure were often significant. No study in a high-income country reported significant landscape, infrastructure, and agricultural factors. For the climatic zone, most of the studies were conducted in tropical countries ($n = 24$) compared to temperate countries ($n = 8$). No study in a temperate country reported statistically significant environmental risk factors related to infrastructure, landscape, and agriculture.

4. Discussion

The present systematic review of 32 publications confirms that the environmental component is a significant risk factor in the leptospirosis transmission pathway. This review demonstrates that risk factors related to water, infrastructure, landscape, agriculture, animal, and occupational exposure are associated with leptospirosis transmission. The combination and interaction of a few components in leptospirosis ecology include environmental drivers and certain types of occupation that support *Leptospira* transmission. As the epidemiology of leptospirosis is complex and varies greatly depending on the environment, an ecological approach is necessary to comprehend disease patterns at the local, regional, and global levels [7].

This study found that water-related factors were associated with an increased risk of leptospirosis infection in all geographical regions except in Europe. However, as only one included study was conducted in Europe, this finding is not representative of the region. Furthermore, due to the deficient number of exposed subjects to water-related activities and exposure to natural water body categories, that particular study had low statistical power, which led to non-significant results [51]. Moreover, animal urine dilution effect might impact the likelihood of contact with Leptospira bacteria in the environment. In contrast with a relatively low dilution of urine in small water bodies such as stagnant water, highly diluted urine and lower pathogen concentrations in big water bodies such as rivers might partially explain why exposure to natural water bodies had non-significant results [60].

The quality of water for daily consumption is critically important. In upper and lower-middle-income countries, water-related risks are usually related to water for everyday use including drinking, washing, and bathing. People who use natural water reservoirs as their primary water source are at higher risk than those whose water is from public taps [31,33,34]. The usage of public water taps provides safe and treated water that reduces the risk of leptospirosis infection. Public water taps are typically treated to eliminate harmful bacteria including *Leptospira,* making it safe to use. Although Raj et al. [34] reported that having water taps as a source of drinking water was a protective factor against leptospirosis infection, it probably served as a confounding factor. This is because the ingestion of water hasn't been demonstrated to be a risk factor. Instead, the potential route of entry for *Leptospira* is through wounds, abrasions, and mucous membranes. However, by using public water taps, individuals are less likely to rely on untreated or potentially contaminated natural water sources.

Exposure to stagnant water [4] such as sewage water [47] and contact with mud [39,49,61] were also risk factors. Although soil, mud, spring water, and sewage water do not act as multiplication reservoirs for pathogenic *Leptospira*, they are temporary carriers and environmental reservoirs that enable disease transmission [62]. Rainfall and flood exposure were also the main drivers of *Leptospira* infection in Asia, South America, and Oceania, which is congruent with previous findings [7,63]. Frequent rainfall will lead to increased vegetated areas, thus increasing rodent abundance in the ecosystem. This will potentially increase the risk of leptospiral environmental contamination [64].

As a result of steadily rising concentrations of greenhouse gases, the global surface temperature will continue to rise and predicted to reach 1.5 °C in the near term (2021–2040). Multiple climate hazards and extreme weather events would unavoidably increase due to global warming, posing various threats to ecosystems and humanity [65]. Almost all regions are predicted to have the risk of coastal and inland flooding due to global warming relative to the pre-industrial period [65]. Heavy rainfall, flooding, and other natural disasters can increase infection risk by disrupting public health services and infrastructure, damaging water and sanitation networks, displacing people, destroying dwellings, and increasing environmental pathogen exposure [11]. The amount of rainfall and the occurrence of leptospirosis are directly correlated [66], making it seasonal in temperate areas and year-round in tropical climates. As climate change leads to extreme precipitation and rising sea levels, extreme weather events such as floods will increase both in rural and urban areas, thus increasing the risk of human leptospirosis infection from exposure to contaminated water [7]. Few leptospirosis outbreaks have been reported in scarce regions, such as the Czech Republic [67] and North America [68], related to climate change.

This review demonstrates that infrastructural deficiencies such as houses with thatched roofs, mud walls, and un-plastered wall houses, particularly in developing countries, are environmental risk factors for leptospirosis. Infrastructural deficiency and inadequate sanitation were predominant in urban slum areas, which are proxies of poverty and low socioeconomic status. We postulate that the higher risk of rat ingression into homes increases the chance of environmental contamination, thus increasing infection risk. Moreover, the absence of proper sewerage systems and the presence of garbage dumping areas were also risk factors for leptospirosis. Lower levels of knowledge and practices regarding leptospirosis prevention may also increase infection risk. This is supported by the findings of Felzemburgh et al. [46], who reported that slum residents had a high chance (>3% per year) of acquiring *Leptospira* infection, with reinfection being common among slum residents with proximity to open sewers. Another important finding was that the risks of primary and secondary infection fell by 46% and 48%, respectively, with every USD1 rise in the daily per capita family income in this community [46]. Living near rubber tree plantations is associated with an increased risk of leptospirosis. This is due to the high concentration of Leptospira found in rubber tree plantations and natural water bodies [37]. Furthermore, many rat species can be found in rubber tree plantations [37,69]. In addition, a favorable tropical climate with high humidity and warm weather in those plantations provides an appropriate niche for organisms to survive longer in the environment.

Besides soil and water being temporary carriers and environmental reservoirs of pathogenic *Leptospira*, many animals play an important role in leptospirosis transmission. The animals involved in disease transmission differ across serovars and geographical areas, and exposure risk is influenced by setting, living circumstances, sanitation, activities, and cultural factors. Exposure to rats and livestock is a significant risk factor in various environment settings, from small islands [41], rural [36,40], and urban communities [40, 51], and slum areas [45,61] to agricultural areas [48,54]. The magnitude of the risk depends on the local prevalence of leptospiral carriage and the degree and frequency of exposure. For example, *Leptospira* prevalence in rats varies greatly depending on geographic location, with some studies reporting a prevalence of >80% in Brazil, India, and the Philippines. On the other hand, studies conducted in Madagascar, Tanzania, and the Faroe Islands have reported zero prevalence of *Leptospira* in rats [70]. A study conducted in a wildlife sanctuary showed that seroprevalence was greater in cattle than in red spiny rats. There was a 62.2% seroprevalence similarity between cattle and red spiny rats [71]. It's conceivable that the leptospires weren't just spread by domestic cattle and rats, but also by other domestic or free-living animals such as several species of carnivores, cetacean, reptilian, and amphibian [72]. Therefore, the spread of *Leptospira* is significant, as it can potentially infect any animal species and is undoubtedly of high importance for human public health.

Although environmental factors have long been recognized as important in human leptospiral infection, occupational exposure has always been significant in middle- and high-income countries. In middle-income countries such as India, Malaysia, Bhutan, American Samoa, and Tanzania, working outdoors was associated with a higher risk of leptospirosis. People who work outdoors such as farmers [41,50], paddy field workers [50], military [58], and agricultural workers [33,38,39] face more chances of getting leptospirosis infection if they come into contact with water, soil or mud contaminated with urine of infected animals. This exposure can happen through cuts and abrasions on the skin, providing potential entry points for the bacteria [39,49]. Occupational exposures were also important in high-income countries, particularly in Oceania. For example, New Zealand has a relatively high incidence of leptospirosis compared to other developed countries. Due to occupational exposure, men have a 9-fold higher risk than women. Compared to other risky occupations such as hunter, veterinarian, technician, stock truck driver, and lake worker, meat processing and farming industry employees had the highest risk from occupational exposure [73]. The magnitude of risk depends on the duration of exposure, the animal type in the exposure, and the worker's task and position in the slaughterhouse. In sheep plants, positive seroprevalence is higher among workers at the slaughter board's beginning and decreases along the slaughter line. Urine splashing during stunning and the subsequent contamination of pelts and carcasses are considered sources of infection, which can be challenging to manage when working with carcasses. Besides, exposure to *Leptospira* from the genitourinary tract organs of the carcass during examination, processing, and evisceration may represent an additional risk of infection [52,57]. Therefore, the vaccination of livestock herds needs to be considered for controlling occupational transmission.

5. Strengths and limitations

This review highlights the importance of the environmental factors associated with leptospirosis transmission. All studies included in this review underwent critical appraisal, and only moderate- to good-quality (score above the average) studies were included. All 32 studies included in this review generally followed the fundamentals of the epidemiological study concept. However, as more than half (62.5%) of the included studies were cross-sectional, our review is subject to the limitation that it may not provide definite information on cause-and-effect relationships. Nevertheless, due to the exclusion criteria of outbreak reports, we believe that the estimation range for risk factors in this review is acceptable, as it was quite harmonized compared to the study design that followed an outbreak that resulted in higher OR [63].

Based on the strict quality appraisal, we excluded the studies that did not mention the type of diagnostic test used. Moreover, the quality score appraisal followed WHO standard laboratory criteria diagnosis and CDC guidelines, ensuring the internal validity of the included studies. Another limitation is that few studies from Europe and North America were included (i.e. only two), rendering the findings not generalizable to these regions. On the other hand, >70% of the included studies were community-based, with appropriate sample size calculation as one of this review's strengths. Lastly, we consider the quality appraisal, which examined the appropriate statistical analysis, a strength of the study. We recommend that future studies clearly define the exposure variable, as most of the studies did not do so.

6. Conclusion

This review shows that the emergence of leptospirosis infection is closely linked to exposure to ecological conditions facilitating transmission. The environmental components related to water, infrastructure, landscape, agriculture, and animal exposure in leptospirosis ecology play an important role in disease transmission. The magnitude of environmental risk factors differs with a geographical region, climate factor, urbanization and population growth, and the country's socioeconomic status. Improvements in sanitation, quality drinking water supply, regular rodent control, and vaccination of livestock and pets are particularly important.

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Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because this study does not involve animal or human participants.

Data availability statement

Data included in article/supp. material/referenced in the article.

CRediT authorship contribution statement

Mazni Baharom: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Norfazilah Ahmad:** Writing – review & editing, Supervision, Conceptualization. **Rozita Hod:** Writing – review & editing, Validation. **Mohd Hasni Ja'afar:** Writing – review & editing. **Fadly Syah Arsad:** Writing – review & editing, Formal analysis. **Fredolin Tangang:** Writing – review & editing. **Rohaida Ismail:** Writing – review & editing. **Norlen Mohamed:** Writing – review & editing. **Mohd Firdaus Mohd Radi:** Writing – review & editing. **Yelmizaitun Osman:** Writing – review & editing.

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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Appendix A. Supplementary data

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