PUBLIC HEALTH RESEARCH

Environmental Determinants of Leptospirosis in Urban Setting: A Systematic Review

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ABSTRACT

Introduction	Leptospirosis is among the neglected infectious diseases with high infection rates and mortality. This disease is largely underreported and underdiagnosed, often difficult to extinguish from other diseases with similar presentation such as Dengue. It is high time for the shift in strategy towards prevention and control particularly with its high prevalence in impoverished urban communities. Thus we aim to systematically review existing literature on the environmental indicators contributing to the risk of getting Leptospirosis in urban settings which is paramount for effective prevention and control.
Methods	A literature search was conducted in December 2021 using Web of Sciences, PubMed, Ovid, and Scopus online databases. Open-access articles produced between 2011 and 2021 were analysed, emphasizing the environmental indicators for Leptospirosis infection in urban settings.
Results	Eight articles met the inclusion benchmarks. The majority of the studies in this review were done specifically in urban slum communities while two studies in Columbia and Puerto Rico consist of the overall urban community. Only three studies assessed environmental indicators as a risk for leptospirosis by using a checklist adapted from published and validated guidelines by the Centre of Disease Control. Adaptation was done to assimilate the characteristics of the area of study. Geography Information System (GIS) was used in four studies to measure and map out the related environmental indicators. One study employ known and verified guidelines to measure environmental risk and produce a prediction score for severe leptospirosis and its discriminative capacity by employing c-statistics derived from the receiver operating characteristic (ROC) curve, sensitivity, and false positivity rates.
Conclusions	Adapting to existing validated and published guidelines in future studies with predictive scoring together with GIS could produce standardized and solid results which then can be replicated in other countries, involving more types of premises other than households such as food premises. Thus, enhanced and focused preventative and control strategies for environmental factors can be undertaken, allowing policymakers to deploy scarce healthcare resources more effectively.

Keywords Leptospirosis; Environmental; Indicator; Risk Factor; Urban

Article history:
Received: 4 January 2024
Accepted: 10 June 2024

INTRODUCTION

Globally, both humans and animals are susceptible to the zoonotic disease Leptospirosis.[1,2] Leptospirosis is transferred to humans by skin wounds and abrasions, or via intact mucous membranes come into touch with any surfaces or elements compromised by an infected animal's urine.[3] Most Leptospirosis infections in humans are asymptomatic, in which nine out of ten appear as a non-specific febrile illness, with the remaining progressing to a severe, deadly disease with multiple organ dysfunction.[4] According to the CDC, the mortality rate for people with severe illness ranges from 5% to 15% and is accompanied by myriads of complication such as renal failure, haemorrhage and jaundice.[5] Leptospirosis affects an estimated one million people severely each year, with a mortality rate of 10% and an increasing number of countries reporting outbreaks and cases.[2,6,7]

Leptospirosis has become an epidemic on a global scale in underdeveloped metropolitan areas[8,9], where rodents shed Leptospires into the soil and water, causing urban transmission.[10] Even though high-risk urban areas for leptospirosis transmission tend to have low social status and bad sanitation, previous studies have shown that they are also very different, with a lot of variation in the social and environmental factors that are linked to the risk of Leptospira transmission.[11,12]

Effective management of urban leptospirosis is hampered by the challenges of executing large-scale sanitation measures in slums, the difficulty of early identification in the absence of a point-of-care diagnostic test,[13] and the lack of a workable human vaccine.[14] It is challenging to implement antibiotic prophylaxis and the use of boots or protective gear in sizable, ongoing at-risk groups.[15] Currently, measures via chemical and enviromental to control rodent populations is the primary technique.[16] To acquire data on rat infestations and architectural flaws that promote rodent populations in cities, surveys of residential exterior spaces, or environmental indicators, are used.[3,4] These solutions, on the other hand, are expensive and have not been standardised, especially in poor nations.

Leptospirosis prevention and rodent control may benefit from targeted, cost-effective interventions that are tailored to homes at high risk of contracting the disease. As a result, we want to systematically review existing literature on the environmental indicators contributing to risk of getting Leptospirosis in urban setting which is paramount for effective prevention and control. We analysed the environmental elements that increase the risk of rodent infestation in high-risk community in this review.

METHODS

The review protocols

The investigation was directed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) review process, which was developed specifically for systematic reviews and meta-analyses.[17] PRISMA's goal is to urge researchers to find the relevant information with the proper amount of detail. On the basis of this review procedure, the authors began their systematic literature evaluation by developing suitable research questions. Three phases comprise the systematic search: identification, screening, and inclusion.

Research questions synthesis

PICO was used to develop the research topic for this study. PICO is a technique that helps authors establish an appropriate research topic. It is based on three basic concepts: population or problem, interest or intervention, context or comparison, and/or outcome.[18] Hence, the review focuses on three primary areas; Leptospirosis (Problem); Indicator (Intervention); environment (COntext); and, guided the authors in formulating its main purpose, as previously stated.

Methods of systematic searching

The systematic search strategy procedure consists of three primary steps: identification, screening, and eligibility (Figure 1).

Identification

Medical Subject Heading (MeSH) phrases and related terms are also searched for in the identification process. The major keywords are Leptospirosis, indicators, environment (Table 1). With the specified databases (Web of Science, Scopus, PubMed, and Ovid) for a literature search, this method will provide a broader coverage of relevant article results. These databases were distinguished by their extensive literature collections, high-quality articles, and powerful search capabilities. There were 2649 articles retrieved from the various databases. There were 411 duplicate articles detected and removed. This process ended with 2238 articles.

Table 1 Systematic search's keywords

Problem	Intervention	Context
Leptospira Canicola*	Indicator	Environment*
Rice-Field Fever	Criteria	
Rice Field Fever	Risk	
Cane Cutter Fever	Factor*	
Cane-Cutter Fever Leptospira		
Infection* Leptospira		
Stuttgart Disease		
Canicola Fever		
Swineherd's Disease*		
Mud Fever		
Leptospiroses		
Leptospirosis		

*asterisk is placed within a word, it serves as a wildcard to search for multiple spellings of a word

Screening

The process of vetting 2,238 items using the sorting function of each database. Included studies should meet the following criteria: (1) The publications appeared in an English-language, peer-reviewed journal; (2) they were published between 2011 and 2021 (10 years); and (3) they pertained to urban settings or communities. Studies were rejected if they were: (1) leptospirosis-related reviews, comments, commentaries, or editorials; (2) articles explaining the study methodology or study design. Two review writers independently selected the included studies. The exclusion of 2209 publications owing to irrelevant population, intervention, or outcome.

Eligibility

Reading the article's title and abstract, the eligibility process seeks to select those papers that meet the study's objectives. 29 articles satisfying the topic of environmental indicators of Leptospirosis were manually sorted. Studies that are irrelevant to the research question and desired outcome will be excluded. In the final selection procedure, only eight items were chosen (Figure 1).

Quality Appraisal

This process used the Mixed method appraisal tool (MMAT) for quality appraisal. MMAT is best to use to evaluate the quality of empirical research which one of the selection criteria for the articles in this study. It required two independent reviewers to appraise these articles. It requires both reviewers to accept the articles to be included in the systematic review. Any disagreement will be discussed among them and final decision will be made. Ultimately, 8 articles were chosen.

Data Extraction & Analysis

Thematic analysis was used because it is seen as a way to synthesise and combine different types of research designs.[19] The thematic analysis is also a descriptive analysis that made it possible to combine data from different types of analyses. These articles that were chosen were carefully studied, paying particular attention to the abstract, approach, results, and commentary. The information was then removed and simplified to provide the results shown in Table 2 based on whether the study was successful in answering its research questions. Only the writers can move on to the thematic analysis after these drawn-out procedures. Each author found patterns in the data they had retrieved from the examined papers, gathered those patterns into a group, and then successfully classified them into various themes in order to provide pertinent themes. The correctness, applicability, and data representation of the theme were once more examined. The developed themes were then presented to a panel of experts that are knowledgeable about both systematic reviews and research in the field of public health. The expert panel came to the conclusion that the themes generated by the review were appropriate and precise.

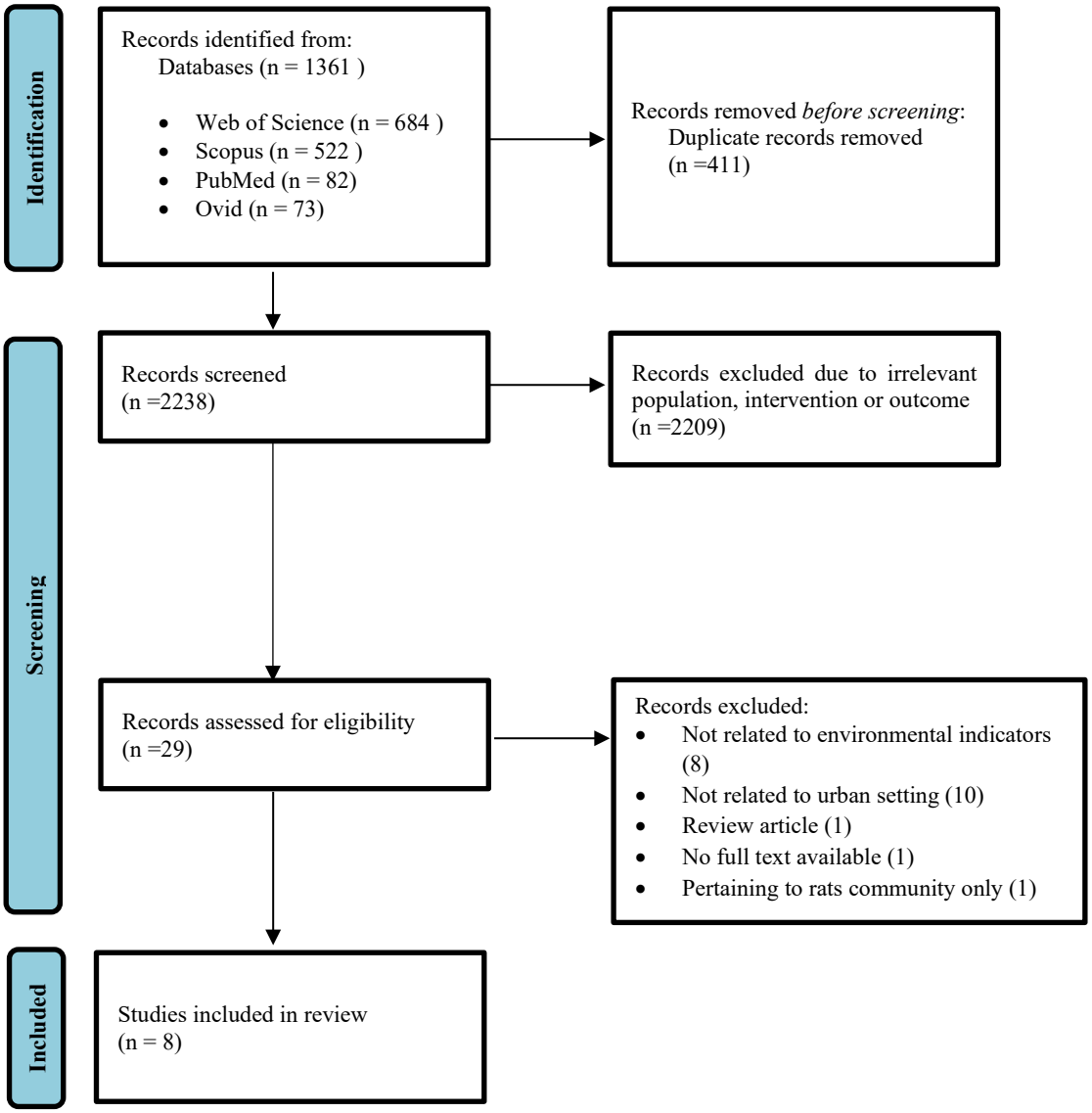

Figure 1 The PRISMA flow diagram

RESULTS

This evaluation includes eight papers published between 2014 and 2021. Majority of the studies involving environmental indicators of Leptospirosis in urban settings originated from Brazil.[8,11,16,20,21] One study was carried out in Malaysia,[22] Puerto Rico[23] and Columbia.[24] Selected articles are consisting of cross sectionals (five), cohort (two) and case-control(one) studies. One study in Salvador, Brazil conducted a case-control comparison between households with laboratory-confirmed leptospirosis and those with no history of clinical leptospirosis, with sample sizes of 95 and 184, respectively.[16] Seroprevalence of leptospirosis were included in six studies,[8,11,20,22-24] laboratory confirmed cases of leptospirosis (severe clinical manifestation) in one study[16] and a study by Santos et al. 2017 in Brazil without any lab investigation, aiming at study area with known case of high incidence rate of severe leptospirosis and asymptomatic Leptospira infection from previous cohort study.[21] Majority of the studies in this review was done specifically in urban slum communities (six) while two studies in Columbia and Puerto Rico consist of the overall urban community. (Table 2)

Table 2 Studies Characteristics

Author/year	Study setting	Study Design	Sample size	Environmental Indicator	Methods	Statistical Analysis	Result/Outcome
Khalil et al, 2021	Urban slum communities (Brazil)	Cross-sectional	1318	• Presence of open sewers near household • Flooding • Trash accumulation in the street • Rat sightings # unclear source of adaptation or validation	Seroprevalence and questionnaire	Structural equation modelling (SEM).	Seroprevalence in the 1,318 participants raged between 10.0 and 13.3%. We found that contact with environmental sources of contamination, rather than presence of rat reservoirs, is what leads to higher risk for residents living in areas with inadequate sanitation. Further, poorer residents may be exposed away from the household, and ongoing governmental interventions were not associated with lower transmission risk. Residents at higher risk were aware of their vulnerability, and their efforts improved the physical environment near their household, but did not reduce their infection chances.
Costa et al, 2021	Urban slum communities (Brazil)	Case-control	Case (n=95); Control (n=184)	• Premise type and details (residential use only, borders on a vacant lot, open sewers <10m distance) • Access to food sources (exposed garbage, animal food, other food and plants, open stores of human food • Access to water (standing water, leaks) • Harbourage for rodents (abandoned vehicles, abandoned appliances, lumber/cutter on grounds, other large rubbish, outbuilding/privies, dilapidated fences and walls, bushes or shrubbery, ornamental plants, presence of exposed earth, built on earthen slope • Entry/access (structural deficiency, unplastered walls) • Rodent active signs (burrows, rodent runs, feces) *Adapted from CDC, 2006	Laboratory confirmed Leptospirosis case in hospital (2007-2009), domiciliary visits were performed retrospectively and prospectively within 3 weeks of clinical leptospirosis confirmation	Conditional regression logistic, conditional logistic regression, predictive score via multivariate analysis, discriminative power of score using c-statistics generated by the receiver operating characteristic (ROC) curve, sensitivity and false positivity rates.	Conditional logistic regression modelling identified the peridomiciliar presence of rodent burrows, rat faeces, runs, households bordering abandoned houses, and unplaster walls as risk factors and developed a predictive score for leptospirosis. A A receiver operating characteristic (ROC) curve analysis evaluated the prediction score performance, with the area under the curve being 0.70 (95% CI, 0.64–0.76) for score development and 0.71 (0.65–0.79) for validation. Results indicate that high proportions of urban slum households are infested with R. norvegicus. The score performed well when identifying high-risk households within slums.
Sahimin et al, 2019	Urban slum communities, (Malaysia)	Cross-sectional	532	• Standard of accommodation • Sources of drinking water • Waste disposal methods • Pet ownership # unclear source of adaptation or validation	Seroprevalence and questionnaire	Maximum likelihood techniques based on log linear analysis of contingency tables	The overall seroprevalence was low (12.6%, with 8.1% being seropositive for anti-Leptospira IgG, indicating previous infection, and 4.9% for anti-Leptospira IgM, indicating current infection) A significant association was recorded between the seropositivity of anti-Leptospira IgG and

							sources of drinking water and no risk factors were linked with the seroprevalence of anti-Leptospira IgM.
Emily et al, 2019	Urban community, (Puerto Rico)	Cross-sectional	202	• Open sewers • Plant debris • Animal food • Standing water • Rodent burrows • Refuse deposits • rats sighted • presence of other animals • frequency and severity of flooding in and around the households • GIS coordinates: Household distance to the canal *Adapted from CDC, 2006	Seroprevalence and questionnaire, household visit for environmental survey	Student's t test, generalized linear mixed model, multivariate regression.	27.2% had Leptospira agglutinating antibodies. Increasing household distance to the canal that runs through the community was associated with decreased risk of infection.
Santos et al, 2017	Urban slum community, (Brazil)	Cross-sectional	221	• Premise type • Food sources for rodents • Water sources for rodents • Harbourage for rodents • Entry/Access for rodents • Signs of rodent infestation • GIS: Household distance to open refuse deposits, open sewage, rainwater drainage systems *Adapted from CDC, 2006	Environmental survey data from a previous nested case control study to identify environmental variables in household with and without evidence of Leptospira transmission	Chi-square, t-test, Generalized additive models (GAM), Multivariate, logistic regression analysis	The general household infestation rate was 45.9%. The risk for rodent infestation was associated with environmental factors supporting harbourage for rats, such as dilapidated fences/walls and households built on an earthen slope. An increase of 1 meter from the nearest sewer was associated with a 3% decrease in the risk of rodent infestation. A lack of sanitation where poor people live provides factors for rat infestation and could the target of educational interventions.
Escandon-Vargas et al, 2017	Urban communities, (Columbia)	Cross-sectional	353	• Toilet location (indoors, outdoors, absence of toilet) • History of house flooding in the previous month • Barefoot walking • Contact with water sources other than aqueduct • Dog ownership • Observation of rodents in the house • Swimming • Travel outside Cali in the previous month	Seroprevalence and questionnaire, household visit for environmental survey	Chi-square ($\chi 2$) test, Student's t test, multivariate logistic regression model	Overall seroprevalence was 12.2%. Factors associated with Leptospira infection were absence of toilet, barefoot walking, travel outside Cali in the previous month, and absence of skin and mucous-membrane lesions in the previous month. Suggests domestic and peridomiciliary transmission of Leptospira likely related to activities of daily living and inadequate environmental conditions.

				• Skin and mucous membrane lesions in the previous month # unclear source of adaptation or validation			
Hagan et al, 2016	Urban slum residents, (Brazil)	Cohort	1730	• Household elevation (1m) • Distance from an open waste sewer (1m) • Vegetation within 10m of home • Accumulated trash within 10m of home • Reporting rats in the peridomicilary environment • Dogs in household • Geographic Information Systems (GIS) were used to obtain tridimensionality distance from subject households to the nearest open drainage systems and accumulated refuse, as well as household elevation # unclear source of adaptation or validation	Seroprevalence and questionnaire, site visit for environmental survey	Mixed effects model (spatiotemporal variation in leptospiral infection), Generalized additive model (GAM)	Infection rate was 35.4 per 1,000 annual follow-up events. Environmental risk factors included rat infestation and lower household elevation. The spatial distribution of infection risk was highly heterogeneous and varied across small scales.
Felzemburgh et al, 2014	Urban slum community, (Brazil)	Cohort	1585	• Rat sightings in household property and workplace in 1 month preceding data collection • Open sewage, rainwater drainage systems and accumulated refuse (proximity) • Presence of dogs, cats, chickens and vegetation within 10 meters of the household. • Geographic Information Systems (GIS) was used to obtain three-dimensional distance from the household to the nearest drainage systems and accumulated refuse, and to the lowest point in the valley (height) # unclear source of adaptation or validation	Seroprevalence and questionnaire, site visit for environmental survey	Chi-square, Wilcoxon rank sum tests, multinomial logistic regression models, hierarchical multinomial multivariate model	Total of 51 Leptospira infections were identified among 1,585 (79%) participants who completed the one-year follow-up protocol. The crude infection rate was 37.8 per 1,000 person-years. The secondary infection rate was 2.3 times higher than that of primary infection rate (71.7 and 31.1 infections per 1,000 person-years, respectively). Proximity of residence to an open sewer and three-dimensional distance of residence to the lowest point in the valley and open waste sewers had a stronger relationship with risk of secondary infection than primary infection.

Environmental Indicator

Adapted from published and validated guideline

Three studies[16,21,23] applied validated checklist adapted from Centre Disease Control[25] pertaining to Integrated Pest Management in conducting urban rodent surveys.[25] CDC systematic checklist includes variable such as premises type (i.e. residential, vacant lot), premises details (i.e. sewers on premises), presence of food sources (i.e. unapproved refuse storage, exposed garbage), presence of water sources (i.e. standing water, leaks), harbourage for rodents (i.e. abandoned vehicles, abandoned appliances, dilapidated nearby building), entry (i.e. structural deficiencies, pipe or wiring gaps) and active signs of rodents (i.e. sightings, droppings, rub marks etc.) According to the environmental and socioeconomic variations observed in the study area, some of the factors were eliminated, adjusted, and/or added.

Costa et al, 2021 additionally added more detailed description regarding premises details which are borders on a vacant lot, open sewers with distance less than 10m from premises and borders on an abandoned house.[16] Pertaining to presence of food sources, open stores of human food is added. Furthermore, regarding the harbourage for rodents, in line with environmental surrounding of the study area and also from literature evidences, exposure to the earth and whether the building is situated on an earthen slope are also considered. Instead of pipe or wiring spaces, unplaster walls are included for rodent ingress and access. In terms rat faeces, this study described in detail the characteristics of faeces according to species of rodents commonly found in the area. Costa et al also included presence of domestic animal such as dogs, cats and also chickens.[16] It was found that, through logistic regression modelling, presence of rodent burrows, rat faeces, runs, households bordering abandoned houses and unplaster walls as risk factors which was then developed into predictive score for leptospirosis. A receiver operating characteristic (ROC) curve analysis was used to evaluate the prediction score's performance. The score performed well in identifying high-risk households in slums, with the area under the curve for score generation being 0.70 (95 percent confidence interval: 0.64-0.76) and for validation being 0.71 (0.65-0.79).[16]

Study by Emily et al 2019, among Cano Martin Pena community, survey the environmental or immediate surrounding household using adapted version of CDC checklist.[23] This community's checklist is limited to open sewers, plant debris, animal food, standing water, rodent burrows, and garbage deposits. Additional environmental indicators or risk factors, such as rat sightings, the presence of other animals, and the frequency and severity of flooding in the vicinity of the homes, were collected via their own questionnaires. Among these environmental indicators, only flooding had a major effect, with people who lived in a home that flooded seldom, sometimes, frequently, or always being 78 percent less likely to be infected with Leptospira than those who resided in a home that never flooded.[23]

Another study in Brazil, by Santos et al. applied adapted version of CDC checklist in area with high incidence rate of severe cases and also asymptomatic Leptospira infection.[21] Similar with study by Costa et al.[16], this study added few criteria under CDC checklist variable in relevance to study area. The following data were considered; the type of premises: borders on an empty lot, open sewer distance of less than ten metres, distance from open sewers, distance from open garbage deposit, level above lowest point in valley, and borders on an abandoned house. In term of presence of food sources, fruit trees and open stores of human food were added. Presence of exposed earth and whether premise was built on earthen slope were added under harbourage for rodents while unplaster walls were included under entry or access for rodents. Rat faeces were described in detail for three common rat species and presence of domestic animals such as dogs, cats and chicken also taken account. The overall household infestation rate for this investigation was 45.9%. Environmental characteristics that encourage rat harbourage, such as crumbling fences/walls and homes constructed on an earthen slope, were linked to the probability of rodent infestation. A one-meter increase in distance from the nearest sewer was linked to a 3% reduction in the likelihood of rat infestation.[21]

Generated from literature evidence

Majority of the studies, studied on environmental indicators or risk factors based on available literature evidence pertaining to rodents' behaviour instead of published and validated guideline. Only four environmental risk factors—open sewers close to homes, flooding, a buildup of rubbish in the streets, and rat sightings—are used by Khalil et al. in their questionnaire from 2021.[20] It was found that, as opposed to the presence of rat reservoirs, people who live in unsanitary areas are more at risk because of their interactions with environmental sources of contamination. Residents with a higher risk of infection knew they were more vulnerable, and they made an attempt to improve the physical environment around their homes, but this did not greatly reduce their risks of infection.[20]

The term "environmental health factors" was used in a Malaysian urban slum study to refer to the standard of living, drinking water sources, waste disposal techniques, and pet ownership. No risk factors were connected to anti-Leptospira IgM seroprevalence, but there was a significant association between anti-Leptospira IgG seropositivity and the source of drinking water.[22]

Escandon Vargas et al. 2017 studied the urban district in Cali, Colombia.[24] The environmental variables are toilet location (indoors, outdoors or absence of toilet), history of flooding, barefoot walking, contact with sources of water besides the aqueduct, dog ownership, the presence of rodents in the home, history of swimming, prior month's travel outside of Cali and prior months' skin and mucous membrane sores. The absence of skin and mucous membrane sores in the preceding month, barefoot walking, travel outside of Cali, and the lack of a toilet were all associated with Leptospira infection. This study reveals that Leptospira transmission in the home and peri domiciliary setting is most likely connected to everyday living activities and suboptimal environmental conditions.[24]

Another study in urban slum of Brazil by Hagan et al., dive on environmental factors that is household related and reservoir related.[8] Household related environment is household elevation, distance from a sewage drain that is open, vegetation within 10 meters of home and accumulated trash within 10 meters of home. Respondents who reported infestations of rats in the peri domiciliary setting and a dog in the home were considered having 'Reservoir related exposures. Rat infestation and lower dwelling elevation were significant environmental risk factors.[8]

In Felzemburgh et al. study, the environmental factors are proximity to open sewage, rainwater drainage systems and accumulated refuse.[11] In addition, respondents were asked if they had seen any rats in their homes or places of employment in the month before the data collection. A household survey was conducted to determine whether there were any dogs, cats, chickens, or plants within 10 metres of the home. There was a larger chance of secondary infection while living next to an open sewer than there was for primary infection. Rat sightings during the day and the presence of rats, as indicated by the largest number of rats seen, were not shown to be risk factors for either primary or secondary infection.[11]

Geographic Information Systems (GIS)

Four studies utilize the Geographic information system (GIS) to further investigate environmental indicator or factor accurately. Emily et al. study area is Caño Martin Peña, a neighbourhood that is surrounded by a canal that overflows after heavy rains.[23] Thus, this study uses GIS coordinates to measure household distance to the canal. It was discovered that increasing residential distance from the community's canal resulted in a lower chance of infection.[23] According to Santos et al., who used GIS to evaluate residential distances to open sewage, open garbage deposits, and rainwater drainage systems, every additional metre of distance from the nearest sewer was associated with a 3% reduction in the likelihood of rat infestation.[21] Hagan et al. used GIS to determine the tridimensionality of a household's distance from the closest open drainage systems and accumulated garbage, as well as the elevation of the home (8). Low household elevation was the only environmental risk factor discovered.[8] Using a geographic information system (GIS), Felzemburgh et al. calculate the three-dimensional distance from a given residence to the closest drainage systems, the lowest point in the valley, and the collected garbage.[11] The three-dimensional distance between the dwelling and the valley's lowest point and the presence of open waste sewers were shown to have a stronger link with the probability of secondary infection than original infection.[11]

Appraisal

Overall, the included studies were of good quality. Five studies were given highest score of 100%,[11,16,20,23,24] while three studies were given the second highest score of 80%.[8,21,22] (Table 3)

Table 3 Quality Appraisal using MMAT

References	3. Quantitative Non- Randomized Studies					Overall Quality Score
	3.1	3.2	3.3	3.4	3.5	
	Are the participants representative of the target population?	Are measurements appropriate regarding both the outcome and intervention (or exposure)?	Are there complete outcome data?	Are the confounders accounted for in the design and analysis?	During the study period, exposure occurred as intended?	
Khalil et al, 2021	Yes	Yes	Yes	Yes	Yes	****
Costa et al, 2021	Yes	Yes	Yes	Yes	Yes	****

Sahimin et al, 2019	Yes	Yes	Yes	Can't tell	Yes	***
Emily et al, 2019	Yes	Yes	Yes	Yes	Yes	****
Santos et al, 2017	Yes	Yes	Yes	Can't tell	Yes	***
Escandon-Vargas et al, 2017	Yes	Yes	Yes	Yes	Yes	****
Hagan et al, 2016	Yes	Yes	Yes	Can't tell	Yes	***
Felzemburgh et al, 2014	Yes	Yes	Yes	Yes	Yes	****

***meet 80% of MMAT criteria
****meets 100% of MMAT criteria

Regional differences in leptospirosis prevalence include hot, humid climates that favour leptospire survival, tropical and subtropical places with significant rainfall, particularly in Latin America and Southeast Asia, and highly endemic regions.[26] Leptospirosis is claimed to be grossly underreported despite the rising incidence and high mortality.[27] Due to underdiagnosis and inadequate disease surveillance, monitoring, and record-keeping in several countries in South East Asia and Southern America, leptospirosis continues to be underreported.[3,28] Additionally, it can be challenging to differentiate between the clinical symptoms of dengue and other endemic diseases that are prevalent in tropical and subtropical regions and share a similar clinical presentation. It is also important to note that most infections are thought be asymptomatic.[4,25] Lack of quick diagnosis is another element that raises the disease's potential risks. Isolation, which carries a significant risk of infection, is used to make the confirmation diagnosis. As a result, we must concentrate on preventing Leptospirosis, as there are several risk factors for the condition. Animal factors, environmental factors, and human factors make up the three primary categories of leptospirosis risk factors.[29] In order to break the chain of infection and stop the transmission of leptospirosis, it's crucial to understand the risk factors that exist within and across these groups. Flooding is a common time for epidemics to occur, and emerging environmental problems and harsh weather patterns may prolong these epidemics.[3] However, environmental exposure through environmental or surrounding sanitation and hygiene is a recognized component causing the disease in addition to environment in terms of weather and climate.[30] As these variables will lead to rodent infestations and increase the likelihood or risk for infection transmission. Thus, it is most prevalent in urban slum settings, where congestion, poverty, and a lack of basic sanitation facilities foster leptospirosis transmission.[11,12,16] However, in this study, where we have conducted a thorough literature assessment of environmental indicators for risk of leptospirosis in urban settings, despite the search of literature review was done for time frame of recent 10 years, it only yielded limited amount if original studies. Looking at the studies included in this review only few studies (there out of eight) adapted their measurement for environmental indicator or risk factor from a validated and published guidelines from CDC. Furthermore, only one study out of these three makes use of it to determine the prediction score of environmental risk for severe leptospirosis and its discriminative capacity utilising c-statistics produced by the receiver operating characteristics (ROC) curve, sensitivity, and false positivity rates. Majority of the studies in this created their version of environmental indicators based on literature evidence pertaining to rodent behaviour. Although most of the studies did follow or consist of the variable theme from CDC standard checklist, such as premises details, presence of food and water source, harbourage for rodents, entry or access via structural deficiencies and actives signs of rodent infestation, however the sub-detail for each theme is different or in other words not standardized. This might be due to the unique characteristics of the study area. Regardless of the difference in detail, standardized and validated variable should be used in combined; with predictive and discrimination score should be more encourage in future studies. The absence of easily accessible epidemiologically based markers for identifying and monitoring residences at elevated risk for leptospirosis has hampered efforts to adopt and improve rodent management measures for urban leptospirosis. According to Costa et al., it may be possible to use five parameters connected to environmental characteristics and objective evidence of rat infestation to pinpoint households living in urban slums who are more likely to have severe leptospirosis. Rat burrows, R. norvegicus faeces, rodent runs, abandoned home boundaries, and unplastered walls were some of these contributing causes. Using a risk score that was

created by averaging the results for each of these factors, homes were divided into subgroups with low, medium, and high leptospirosis incidence risks. The most active chemical rodent control, environmental treatments, and educational initiatives may be helpful for households identified as moderate- or high-risk.[16] Additionally, geographic information systems (GIS) and maps of the target area or community are greatly valued tools. Maps assist in defining the infestation problem and its causes, as well as tracking progress toward eradication. Programs frequently employ maps of the target region to assign block inspections, illustrate evolving patterns in infestations and their causal factors, and track progress toward resolving the rodent problem.[25] Other causal factors, such as water supplies and entry and exit routes, may be mapped. These maps can be used to highlight necessary corrective action.[25,31] Nonetheless, in this review, we only found four studies utilizing GIS to measure environmental factors.

Limitation

The fact that we restricted our search to Scopus, Web of Science, Ovid, and Pubmed may have reduced the number of studies that were possibly relevant, which is a drawback of this review. Additionally, we only looked at English-language articles. The completion of a thorough assessment is further hampered by the lack of an international standard standards checklist for environmental indicators and the significant variation between study designs.

CONCLUSION

Leptospirosis cases being under-reported and underdiagnosed, at the same time with high rate of infection and mortality particularly involving impoverished urban communities, it is high time that strategies should be shifted towards prevention and control in term of modifiable environmental risk. Adapting to existing validated and published guideline in more future studies with predictive scoring together with GIS could produce standardized and solid result which then can be replicated in other countries, involving more type of premises other than household such as food premises. Thus, governments may implement targeted and enhanced environmental factor preventive and control measures while also being better able to allocate the scarce healthcare resources.

ACKNOWLEDGEMENTS

This study is supported by the Department of Community Health at Universiti Kebangsaan Malaysia (UKM). UKM is not responsible for any use of the information contained in this publication, which only reflects the viewpoints of the authors.

Author Contributions

The creation and execution of the research plan, data analysis, and paper authoring were all contributions from all authors.

Funding

There was no specific grant from a funding organisation in the public, commercial, or not-for-profit sectors for this research.

REFERENCES

1. AL kattan G, Abdul Rani Bahaman, Siti Khairani Bejo, Zakaria Z, Garba B. Serological and molecular prevalence of Leptospira infection in Rat populations in Kuala Lumpur. *Australian Journal of Basic and Applied Sciences.* 2017.
2. Hartskeerl RA, Collares-Pereira M, Ellis WA. Emergence, control and re-emerging leptospirosis: dynamics of infection in the changing world. *Clin Microbiol Infect.* 2011;17(4):494-501.
3. Leptospirosis: Fact Sheet. wwwwhoint.
4. Centers for Disease C, Prevention. *LEPTOSPIROSIS Fact Sheet for Clinicians Background.* 2018.
5. Bharti AR, Nally JE, Ricaldi JN, Matthias MA, Diaz MM, Lovett MA, et al. Leptospirosis: a zoonotic disease of global importance. *Lancet Infect Dis.* 2003;3(12):757-71.
6. Abela-Ridder B, Sikkema R, Hartskeerl RA. Estimating the burden of human leptospirosis. *Int J Antimicrob Agents.* 2010;36 Suppl 1:S5-7.
7. Picardeau M. Diagnosis and epidemiology of leptospirosis. *Med Mal Infect.* 2013;43(1):1-9.
8. Hagan JE, Moraga P, Costa F, Capian N, Ribeiro GS, Wunder EA, Jr., et al. Spatiotemporal Determinants of Urban Leptospirosis Transmission: Four-Year Prospective Cohort Study of Slum Residents in Brazil. *PLoS Negl Trop Dis.* 2016;10(1):e0004275.
9. Kyobutungi C, Ziraba AK, Ezeh A, Yé Y. The burden of disease profile of residents of Nairobi's slums: results from a demographic surveillance system. *Popul Health Metr.* 2008;6:1.
10. Costa F, Wunder EA, Jr., De Oliveira D, Bisht V, Rodrigues G, Reis MG, et al. Patterns in Leptospira Shedding in Norway Rats (Rattus norvegicus) from Brazilian Slum Communities at High Risk of Disease Transmission. *PLoS Negl Trop Dis.* 2015;9(6):e0003819.
11. Felzemburgh RD, Ribeiro GS, Costa F, Reis RB, Hagan JE, Melendez AX, et al. Prospective study of leptospirosis

transmission in an urban slum community: role of poor environment in repeated exposures to the Leptospira agent. *PLoS Negl Trop Dis.* 2014;8(5):e2927.
12. Reis RB, Ribeiro GS, Felzemburgh RD, Santana FS, Mohr S, Melendez AX, et al. Impact of environment and social gradient on Leptospira infection in urban slums. *PLoS Negl Trop Dis.* 2008;2(4):e228.
13. McBride AJ, Athanazio DA, Reis MG, Ko AI. Leptospirosis. *Curr Opin Infect Dis.* 2005;18(5):376-86.
14. Ko AI, Goarant C, Picardeau M. Leptospira: the dawn of the molecular genetics era for an emerging zoonotic pathogen. *Nature Reviews Microbiology*. 2009;7(10):736-47.
15. Phraisuwan P, Whitney EA, Tharmaphornpilas P, Guharat S, Thongkamsamut S, Aresagig S, et al. Leptospirosis: skin wounds and control strategies, Thailand, 1999. *Emerg Infect Dis.* 2002;8(12):1455-9.
16. Costa F, Zeppelini CG, Ribeiro GS, Santos N, Reis RB, Martins RD, et al. Household rat infestation in urban slum populations: Development and validation of a predictive score for leptospirosis. *PLoS Negl Trop Dis.* 2021;15(3):e0009154.
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj.* 2021;372:n71.
18. Pollock A, Berge E. How to do a systematic review. *Int J Stroke.* 2018;13(2):138-56.
19. Flemming K, Booth A, Garside R, Tunçalp Ö, Noyes J. Qualitative evidence synthesis for complex interventions and guideline development: clarification of the purpose, designs and relevant methods. *BMJ Glob Health.* 2019;4(Suppl 1):e000882.
20. Khalil H, Santana R, de Oliveira D, Palma F, Lustosa R, Eyre MT, et al. Poverty, sanitation, and Leptospira transmission pathways in residents from four Brazilian slums. *PLoS Negl Trop Dis.* 2021;15(3):e0009256.
21. Santos NJ, Sousa E, Reis MG, Ko AI, Costa F. Rat infestation associated with environmental deficiencies in an urban slum community with high risk of leptospirosis transmission. *Cad Saude Publica.* 2017;33(2):e00132115.
22. Sahimin N, Sharif SA, Mohd Hanapi IR, Nai Chuan S, Lewis JW, Douadi B, et al. Seroprevalence of Anti-Leptospira IgG and IgM Antibodies and Risk Assessment of Leptospirosis among Urban Poor Communities in Kuala Lumpur, Malaysia. *Am J Trop Med Hyg.* 2019;101(6):1265-71.
23. Briskin EA, Casanovas-Massana A, Ryff KR, Morales-Estrada S, Hamond C, Perez-Rodriguez NM, et al. Seroprevalence, Risk Factors, and Rodent Reservoirs of Leptospirosis in an Urban Community of Puerto Rico, 2015. *J Infect Dis.* 2019;220(9):1489-97.
24. Escandón-Vargas K, Osorio L, Astudillo-Hernández M. Seroprevalence and factors associated with Leptospira infection in an urban district of Cali, Colombia. *Cad Saude Publica.* 2017;33(5):e00039216.
25. Centers for Disease Control and Prevention (CDC). *Integrated Pest Management: Conducting Urban Rodent Surveys i.* 2006.
26. Garba B, Bahaman AR, Bejo SK, Zakaria Z, Mutalib AR, Bande F. Major epidemiological factors associated with leptospirosis in Malaysia. *Acta Trop.* 2018;178:242-7.
27. Benacer D, Thong KL, Verasahib KB, Galloway RL, Hartskeerl RA, Lewis JW, et al. Human Leptospirosis in Malaysia: Reviewing the Challenges After 8 Decades (1925-2012). *Asia Pac J Public Health.* 2016;28(4):290-302.
28. Pappas G, Papadimitriou P, Siozopoulou V, Christou L, Akritidis N. The globalization of leptospirosis: worldwide incidence trends. *Int J Infect Dis.* 2008;12(4):351-7.
29. Sakundarno M, Bertolatti D, Maycock B, Spickett J, Dhaliwal S. Risk factors for leptospirosis infection in humans and implications for public health intervention in Indonesia and the Asia-Pacific region. *Asia Pac J Public Health.* 2014;26(1):15-32.
30. Kamath R, Swain S, Pattanshetty S, Nair NS. Studying risk factors associated with human leptospirosis. *J Glob Infect Dis.* 2014;6(1):3-9.
31. Rahayu S, Sakundarno Adi M, Dian Saraswati L. Mapping Of Leptospirosis Environmental Risk Factors and Determining the Level of Leptospirosis Vulnerable Zone In Demak District Using Remote Sensing Image. *E3S Web Conf.* 2018;31:06003.