

# BMJ Open Environmental risk factors of leptospirosis in urban settings: a systematic review protocol

Mohd Hatta Abdul Mutalip,<sup>1</sup> Mohd Amierul Fikri Mahmud,<sup>1</sup> Noor Aliza Lodz,<sup>1</sup> Norzawati Yoep,<sup>1</sup> Eida Nurhadzira Muhammad,<sup>1</sup> Ahzairin Ahmad,<sup>2</sup> Mohd Hazrin Hashim,<sup>1</sup> Nor Asiah Muhamad<sup>1</sup>

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<sup>1</sup>Center for Communicable Disease Research, Institute for Public Health, Kuala Lumpur, Malaysia

<sup>2</sup>Center for Non-Communicable Disease Research, Institute for Public Health, Kuala Lumpur, Malaysia

## Correspondence to

Mohd Hatta Abdul Mutalip; [hatta.mutalip@gmail.com](mailto:hatta.mutalip@gmail.com)

## ABSTRACT

**Introduction** Leptospirosis is the most common zoonotic disease that causes morbidity and mortality worldwide. The disease can cause sporadic epidemics and recent epidemics have become more apparent in urban localities. There is lack of documented evidence on the specific risk factors of leptospirosis infection among the urbanites, thereby impeding initiatives for prevention in urban settings. We aim to systematically search published articles and synthesise evidence on the risk factors associated with leptospirosis infection among the susceptible populations in urban localities, particularly to identify the risk factors of non-recreational leptospirosis infection.

**Methods and analysis** We will conduct a systematic review of observational studies that investigated environmental risk factors of leptospirosis in urban localities. The search will be performed for any eligible articles from selected electronic databases from 1970 until May 2018. The study will include any studies that investigated risk factors of confirmed leptospirosis cases who acquired the infection in urban locality, particularly exposures from the non-recreational and non-water-related activities. Study selection and reporting will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and Meta-Analysis of Observational Studies in Epidemiology guideline. All data will be extracted using a standardised data extraction form and quality of the studies will be assessed using the Newcastle-Ottawa Scale guideline. Descriptive and meta-analysis will be performed by calculating the standardised median ORs and risk ratios for types of the non-recreational risk factors stratified by social, living conditions and environmental exposures, types of reservoirs and transmissions and types of activities and employments associated with leptospirosis infection in urban locality.

**Ethics and dissemination** No primary data will be collected thus no formal ethical approval is required. The results will be disseminated through a peer-reviewed publication and conference presentation.

**PROSPERO registration number** CRD42018090820.

## INTRODUCTION

### Background

Leptospirosis is a zoonotic disease caused by spirochaete bacteria in the genus *Leptospira*. The disease is widespread in the environment with worldwide distributions.<sup>1–3</sup> The wide

## Strengths and limitations of this study

- This review specifically will include studies on leptospirosis infection particularly related to non-recreational activities in urban areas.
- The review will systematically retrieve and document all observational studies in accordance to a standard guideline for data collection and reporting of findings.
- Meta-analysis will be used to provide evidence and increase the precision of the quantitative estimates of exposures related to leptospirosis infection in urban areas.
- This study will exclude any interventions or community trials pertaining to leptospirosis control.
- Prevalence and incidence rates of urban leptospirosis will be spatially mapped to illustrate the global burden of leptospirosis in urban areas.

spectrum of this disease ranges from subclinical, mild and self-limited febrile illness to severe syndrome of multi-organ infection attributable to high mortality. The disease produces signs and symptoms characterised by headaches, fever, jaundice and complications such as kidney and liver failure. The burden of leptospirosis is underestimated due to lack of awareness of the disease, low access to rapid diagnostics<sup>4</sup> and limitations in surveillance system in many countries especially countries in temperate zone and low-resource settings.<sup>1 3</sup> In endemic areas, human leptospirosis infections usually presents itself with mild symptoms or even asymptomatic at times<sup>2</sup> and confirmed leptospirosis are more apparent among patients with acute undifferentiated fever.<sup>4</sup> Early diagnosis is challenging as the disease presents non-specific symptoms and indistinguishable from other tropical acute febrile illness.<sup>2 4</sup> Since there is no available vaccination, prevention and treatment are the most effective way to combat leptospirosis infection.

The mortality associated with *Leptospira* infection attributed to high burden of mortality with 58 900 deaths and 2.90 million disability adjusted life years compared with other tropical diseases.<sup>5</sup> Recent study estimated leptospirosis infection had caused more than 1 million cases per year and the disease morbidity is more prevalent among the rural populations and widely distributed in the tropical regions.<sup>3</sup>

Small mammals are known for leptospiral renal carriage.<sup>4</sup> *Leptospira* has been isolated from small mammals such in rodents, bats, marsupials and rodents have become important reservoirs for leptospirosis.<sup>4 6</sup> All these small mammals especially rodents are ubiquitous in environment and disease transmission is greatly influenced by environmental conditions affecting the biology, behaviour, or abundance of spirochaetes and their hosts.<sup>4</sup>

Leptospirosis was always known as an occupational disease where human acquire leptospirosis infection primarily from occupational exposure.<sup>2</sup> Activities such as mining, sewer maintenance, livestock farming, agricultural and military manoeuvres are at risk for leptospirosis infection.<sup>2 4</sup> Incidence related to occupational exposure is preventable by implementation of policy on control measures by using personal protective equipment.<sup>2</sup> In developed countries, more cases of point-source outbreaks occurred due to participating in recreational and water-related activities.<sup>2 7 8</sup> In addition, there were cases associated with adventurous jungle activities including hiking, caving and extreme sports.<sup>2</sup>

Leptospirosis is well-known as a rural disease but infection could also occur in urban settings which is associated with poor urban slums.<sup>1 4 9</sup> These vulnerable population acquire leptospirosis infection from direct or indirect contact with rats and poor environment settings where sanitation and hygiene are compromised.<sup>1</sup> However, the dynamism and transmission of the disease has shifted with more sporadic outbreaks reported in the inner city due to climatic factor, rapid urbanisation and development.<sup>9</sup> In recent years, the emergence and expansion of leptospirosis in urban areas have been seen in developed countries, notably European countries.<sup>10</sup> Improper waste management and accumulation of garbage attract rats' infestation, which is connected with leptospirosis infection among the urbanites.<sup>10</sup> Urban leptospirosis is also associated with extreme weather events such as flooding and heavy rainfalls facilitating the dispersal of leptospores shedding in urban environment.<sup>1 8 11</sup> Flooding may also influence the dispersion of rats unto the human population that consequently increases the risk of incidental infection in human and domestic animals.<sup>8</sup>

### Why is it important to do this review?

Leptospirosis has become an urban health problem where epidemics sporadically distributed in inner city associated with rats exposure.<sup>12</sup> In recent years, there were more cases of leptospirosis reported among the urbanites who resided in proper housing infrastructure and the disease is prevalent among those with no history of participating

in recreational or water related activities.<sup>8 10</sup> In urban setting, most studies investigated urban slums and geographical conditions that associated with leptospirosis infection.<sup>13-16</sup> However, to our present knowledge, there are no documented reviews which explicitly discussed or synthesised current available evidence on general urban leptospirosis infection especially of those who acquired infection from the non-recreational exposures or patients who did not participate in water-related activities. We believe a comprehensive systematic review could provide the best available evidence on urban leptospirosis and its associated risk factors, particularly evidence on leptospirosis infection from the non-recreational exposure or non-water related activities. This review is essential for the public health authority to conduct environmental health assessment, to plan activities for environmental surveillance and control to mitigate urban leptospirosis in household and peridomiliary in the urban settings.

### Objectives

To identify potential environmental risk factors associated with leptospirosis infection among the urbanites. This review will explicitly synthesises information on environmental risk factors related to non-recreational exposures, types of reservoirs for *Leptospira* and mode of transmission of leptospirosis in the urban settings and also to further explore types of activities associated with leptospirosis infection among the urbanites. This review will also identify prevalence or incidence of urban leptospirosis and when data are available, we will identify types of leptospirosis serovars in the urban settings.

### Review questions

For patients who are diagnosed and confirmed leptospirosis, we would retrospectively seek their exposure(s):

1. What are the non-recreational risk factors associated with leptospirosis infection among children and adults who live in the urban area?
2. What reservoirs associated with leptospirosis infection among children and adults who live in the urban area?
3. What activities associated with leptospirosis infection among children and adults who live in the urban area?
4. What are the incidence rates or prevalence of leptospirosis in urban setting?

We will also retrieve articles on surveillance reports or field research studies that investigated risk factor(s) of leptospirosis in the urban environment:

1. What types of samples that is positive with the *Leptospira* spp in urban environment?
2. What is the predominant *Leptospira* spp in urban environment and their associated reservoirs?

### METHODS

We will conduct a systematic review in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.<sup>17</sup> As this systematic review will rigorously review observational study designs with meta-analysis as the outcome, we will integrate our reporting with the

Meta-Analysis of Observational Studies in Epidemiology guideline.<sup>18</sup>

### Patient and public involvement

Patients and or public were not involved in this study as this is a systematic review protocol.

### Eligibility criteria

#### Types of studies

This systematic review will review published articles restricted to observational study designs include cohort, case-control, cross-sectional and ecological studies. We will also include case reports, surveillance and outbreak reports, which describe on the risk factors associated with leptospirosis infection. We will exclude reviews and randomised control trials study designs in this review. However, we will retrieve any eligible articles from the selected review articles to include in this review.

#### Population

This review will include all children and adults living in urban area and diagnosed with confirmed leptospirosis. This review will restrict published articles reported of leptospirosis cases from the rural settings or anyone who acquired leptospirosis infection in the urban from recreational or water-related activities. According to Medical Subject Headings (MeSH) search terms, rural setting is defined any inhabitants of rural areas or of small towns with other entry term(s) such as rural communities or rural spatial distribution.

#### Types of exposures

We will include any types of exposures associated with leptospirosis infection among the urbanites. The exposures include any activities or exposures other than participating in recreational activities such as water activity: swimming, sailing, kayaking, wading and rafting, caving, fishing. We will also exclude any activities related to participating in jungle adventure trips, or outdoor sports activities. As we excluded cases from rural area, so any exposures related to vegetable farming or animal farming and agriculture will be excluded from this review.

#### Types of outcome measures

The outcome of this review are the environmental exposures of confirmed human leptospirosis case in urban settings and we will follow the standard case definitions by the WHO<sup>19</sup> and Centers for Disease Control and Prevention guidelines.<sup>20</sup> Confirmed leptospirosis is defined by a description of clinical signs or symptoms with laboratory confirmation (see online supplementary appendix 1). We will also tabulate any incidence or prevalence of human leptospirosis from urban settings that fulfil the inclusion criteria of this review.

Secondary outcome measure would be on the information for the types of *Leptospira* serovars in urban settings as reported in any clinical specimens from animals or environmental samples.

### Information sources

#### Electronic searches

We will systematically conduct a comprehensive literature search using various databases including PUBMED, EMBASE, Web of Science and EBSCOhost to identify potential studies. We will retrieve eligible published articles from 1970 until May 2018. We will adapt the search strategy with the key elements in research question: population, exposure, comparator, outcome and study design (online supplementary appendix 2). Two main approaches for search strategy include searching using the MeSH terms and free-text terms in the title and abstract on databases (online supplementary appendix 3). An example of a search strategy for the PUBMED database is also shown in online supplementary appendix 3. This review will identify potential studies without language restrictions and we will translate the non-English languages abstracts and articles for inclusion in this review. We will also check reference lists from all reviews related to the inclusion criteria.

#### Selection of studies

Two reviewers will screen the titles and abstracts independently, record and import search results of their findings in EndNote X7 (Clarivate Analytics). All articles will be classified for inclusion, or exclusion based on the eligibility of this review and further checked for duplication. Full-text article will be retrieved if the study is unclear from the title and/or abstract. Relevant articles will be further confirmed for inclusion through full-text review. The third reviewer will resolve discrepancies between reviewers. Finally, three reviewers will discuss their findings where all eligible articles will be cross-checked for inclusion criteria from various selected databases.

#### Data extraction

Reviewers will use a standardised data extraction form that will be piloted in this review. Two authors will extract the study characteristics, quantitative data (findings on the exposures) and outcome data from included studies. The variables of data extraction form as described as follows:

- ▶ Title, author and year.
- ▶ Methods: study design, setting, study location, withdrawals and study period, method of analysis.
- ▶ Participants: sample size, mean age or age range, gender.

Types of exposures: non-recreational or recreational, description of exposures and risk/associated factors, comparison including control condition:

- ▶ Outcomes: description of leptospirosis for diagnosis outcome, clinical information, types of laboratory testing, laboratory findings, serological information.

#### Quality assessment

Two authors will independently check each selected article to minimise bias. All selected articles will be examined for methodological quality using the Newcastle-Ottawa Scale (NOS) in non-randomised studies of interventions<sup>21</sup> and



risk of bias in non-randomised studies of intervention (ROBINS-I) which will be incorporated together.<sup>22</sup> The NOS composed of all these aspects: selection, comparability and exposure or outcome. The maximum score is nine points where studies with NOS score <3 is classified poor, NOS score between 3 and <7 considered moderate and NOS scores  $\geq 7$  is classified high quality.<sup>21</sup> We will also incorporate a quality assessment criteria checklist for disease incidence studies adopted from the Leptospirosis Burden Epidemiology Research Group, WHO.<sup>23</sup> Two authors will independently assess the risk of bias for each study according to the criteria incorporated between NOS and ROBINS-I. We will include studies with potential high risk of bias. We will judge each potential source of bias as high low or unclear and provide a quote from the study report together with justifications for our judgement in the risk of bias in included studies table.

### Summary of findings table

The primary outcome of this review will be the arrays of environmental exposures associated with urban leptospirosis and secondary outcome would be the identification of *Leptospira* serovars in urban settings. Hence, we will create a ‘Summary of Findings’ table by tabulating the following exposures: (1) environmental including geography; (2) social and living conditions; (3) animals; (4) activities; (5) employments and (6) serological information of *Leptospira* in urban settings.

We will assess the quality of evidence for all outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The GRADE elements consist of study limitations, consistency of effect, indirectness, imprecision and publication bias.

### Data analysis and statistical analysis

We will conduct descriptive data analysis using statistical software (StataCorp). When data are available, we will tabulate data on proportions, prevalence, or counts on the urban leptospirosis cases or incidences and serological information of urban *Leptospira*. We will spatially map the distribution of urban leptospirosis cases together with the serological classification of *Leptospira*.

Dichotomous exposure measures presented in OR, risk ratio (RR) or prevalence OR with the corresponding 95% CIs will be tabulated by:

- i. Types of non-recreational risk factors stratify by employments, social and living conditions and environmental exposures.
- ii. Types of reservoirs and transmissions for leptospirosis infection in urban.
- iii. Types of activities associated with leptospirosis infection.

We will perform meta-analysis by calculating the pooled ORs and RRs using the random effects model for types of the non-recreational risk factors stratified by social, living conditions and environmental exposures, types of reservoirs and transmissions and types of activities

and employments associated with leptospirosis infection in urban locality. We will convert all the ORs to RRs according to Wang<sup>24</sup> and Grant.<sup>25</sup>

### Assessment of reporting biases

Publication bias will be assessed by the Bregg’s rank correlation and Egger’s weighted regression methods<sup>26</sup> and we will further create and examine the funnel plots for publication bias.

### Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. The conclusions can be used as guidelines for health authority in the control and preventative activities. Our implications for research will suggest priorities for future research and outline the remaining uncertainties in the area.

### Ethics and dissemination

We will register this systematic review with the National Medical Research Register, Ministry of Health Malaysia. This protocol will be registered with the PROSPERO. We plan to use the findings of this review to update the checklist of Leptospirosis outbreak investigation form. All findings will be shared and disseminate at any local or international conference, including preliminary findings to the Local Municipal Councils and Disease Control Division of Ministry of Health Malaysia.

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**Contributors** Conceiving the protocol: MHAM and MAFM. Designing the protocol: MHAM and AA. Coordinating the protocol: MHAM. Designing search strategies: MHAM, NAL, NY, MAFM, MHH, ENM. Writing the protocol: MHAM and NAL. Providing general advice on the protocol: NAM.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** No ethical approval is necessary, as we don’t collect primary data that require formal ethical assessment.

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