


# BMJ Open Distribution, frequency and clinical presentation of leptospirosis and coinfections: a systematic review protocol

Eliana L Parra Barrera ,<sup>1,2,3</sup> Solmara Bello,<sup>2,4</sup> Gina M Gallego-Lopez,<sup>5,6</sup> Nicolhole Atero,<sup>7</sup> Elizabeth Reyes Santamaría,<sup>8,9</sup> Adriana Bautista<sup>10</sup>

**To cite:** Parra Barrera EL, Bello S, Gallego-Lopez GM, *et al.* Distribution, frequency and clinical presentation of leptospirosis and coinfections: a systematic review protocol. *BMJ Open* 2022;**12**:e055187. doi:10.1136/bmjopen-2021-055187

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-055187>).

Received 16 August 2021  
Accepted 09 November 2022

## ABSTRACT

**Introduction** Leptospirosis is a zoonotic disease with high prevalence in low-income and middle-income countries and tropical and subtropical regions. The clinical symptoms of the disease are similar to symptoms presented by other endemic infectious diseases that could be present simultaneously. Thus, leptospirosis could be masked by similar infections like dengue, malaria, hantavirus, melioidosis and borreliosis, among others. Therefore, leptospirosis could present itself as an under-reported infection or as a coinfection with another pathogen, as has been reported in the literature. However, there is a lack of documented evidence about the specific risk factors of leptospirosis infection, the symptoms, the coinfection's mortality and the frequency of coinfection. Additionally, leptospirosis coinfections have not been considered a neglected public health concern. Therefore, this systematic review aims to evaluate published articles that show the risk factors associated with leptospirosis infection and coinfection with other pathogens.

**Methods and analysis** The search process to identify eligible studies will be conducted including the LILACS, ProQuest, PubMed and Scopus databases with no restriction in terms of publication date. Also, grey literature will be included in the research. Authors will independently screen the title and abstracts of the articles identified from the search using Rayyan free software. Eligibility criteria include peer-reviewed research articles written in English or Spanish, including observational studies, cohorts, case-control, cross-sectional, ecological studies and report cases. The systematic review will include studies that report descriptions of leptospirosis cases with coinfection or co-occurrence. The search will be accomplished by articles from 1950 to May 2022. The data will be extracted in a standard extraction form using an Excel format.

**Ethics and dissemination** Results will be published in a peer-reviewed journal. Also, findings will be disseminated through scientific meetings. Ethical approval will not be required as this is a systematic review and primary data will be not collected or included.

**PROSPERO registration number** CRD42021234754.

## INTRODUCTION

Leptospirosis is a zoonotic disease caused by spirochaete bacteria *Leptospira* and constitutes a neglected tropical disease with worldwide distributions.<sup>1,2</sup> In 2015, it was estimated that

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Coinfection of leptospirosis can influence epidemiology and disease severity.
- ⇒ This systematic review will provide evidence of available leptospirosis cases and coinfections.
- ⇒ The identification of early signs and symptoms would help improve the treatment and avoid complications in patients.
- ⇒ Results of this work will be disseminated to scientific and medical staff.
- ⇒ Data will be used to provide evidence and increase the precision of the evolution of leptospirosis and in cases with coinfections.
- ⇒ We expect to systematically describe the confirmation leptospirosis methodology and the clinical presentation of the cases or studies.

1,03 million leptospirosis cases occur annually with a global burden of 58 900 deaths<sup>3</sup> and 2.90 million disability-adjusted life-years annually, affecting especially the tropical and endemic areas.<sup>3,4</sup> However, the burden of leptospirosis is still underestimated due to a lack of awareness of the disease, and low access to screening and confirmation tests, as a result of several limitations in surveillance systems in many countries.<sup>1,5–10</sup>

Leptospirosis symptoms have a wide spectrum that ranges from subclinical, mild and self-limited febrile illness to a severe syndrome of multiorgan infection that could be attributable to high mortality.<sup>4,9,11–13</sup> Human leptospirosis infection usually is initiated as acute undifferentiated fever.<sup>13,14</sup> Then the infection presents a wide variety of symptoms (eg, headaches, jaundice and complications such as kidney and liver failure)<sup>9</sup> that also occur in other infectious diseases.<sup>15</sup> As leptospirosis is more frequent in tropical countries, it could be present simultaneously with other febrile syndromes induced by malaria, dengue,<sup>16,17</sup> Zika,<sup>18</sup> chikungunya and hantavirus, among others.<sup>7,19</sup> Therefore, early diagnosis is



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For numbered affiliations see end of article.

### Correspondence to

Dr Eliana L Parra Barrera; [elipabarrera@yahoo.es](mailto:elipabarrera@yahoo.es)

challenging as the disease presents non-specific symptoms and is indistinguishable from other tropical acute febrile illnesses.<sup>15 20</sup>

There is epidemiological synergy between leptospirosis outbreaks and other aetiologies such as viral infections including chikungunya, dengue<sup>16 21</sup> and Zika,<sup>18</sup> parasitic infections such as malaria or babesia, and bacterial infections such as rickettsiosis,<sup>7</sup> borreliosis and melioidosis,<sup>22</sup> resulting in human coinfections. Despite the importance of leptospirosis and its coinfections and its potential impact on public health, we know little about the occurrence and consequences of such coinfections. Thus, the objective of this study is to review the impact of leptospirosis coinfection on human clinical disease, discuss the possibility of cotransmission and describe the transmission dynamics of cotransmission.

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

Leptospirosis has become an important neglected disease worldwide due to the increase of cases, outbreaks and worldwide distribution. Since there is no vaccine available,<sup>23</sup> prevention and treatment are the most effective way to combat leptospirosis infection. There are also, several knowledge gaps, especially in the leptospirosis burden, distribution and risk factors which are limitations for disease treatment, prevention and control.<sup>3 4 11</sup> Also, leptospirosis is an undifferentiated febrile infection like other febrile diseases.<sup>2 14 24</sup> In the last years, several reports, studies, outbreaks and research have reported coinfection with febrile diseases.<sup>7 16–19 21</sup> However, to our knowledge, there is no documented literature or currently available evidence that summarises all the possible coinfections with leptospirosis. Also, there is not enough information about the patient course or outcome, the diagnosis used to report coinfection, the confirmation techniques used for coinfection with leptospirosis, the results of treatment in patients with coinfection or increased mortality due to coinfection. We believe this could be a comprehensive systematic review to provide the best available evidence on the frequency and worldwide distribution of the coinfection with leptospirosis. This review could be essential for the epidemiology, clinical and public health procedures to conduct decisions on health assessment, and control to mitigate the complication or the death of the patients or as a line of data for the clinical predictors of leptospirosis coinfection with febrile infections.

### Objectives

To identify the coinfections more frequently found with leptospirosis worldwide, and to determine if leptospirosis coinfections could affect the patient's health, the clinical outcome and the treatment compared with infection with *Leptospira* alone. As well as, to investigate whether the clinical course of leptospirosis could be modified by the coinfection. This review will also identify the frequency of the coinfection by location.

### Review questions

1. What is the most frequent coinfection associated with leptospirosis cases worldwide?
2. What is the distribution of the leptospirosis cases with coinfections by location?
3. What are the symptoms and signs associated with leptospirosis and coinfections? Does coinfection alter clinical disease?
4. What are the incidence rates, prevalence and mortality rates of leptospirosis when it occurs with a coinfection?
5. What is the treatment (antibiotic, hospitalisation or/and Intensive Care Unit) developed for leptospirosis coinfections, and what is the most effective?

### METHODS

In the development of this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement will be used.<sup>25</sup> Also, we will review rigorously epidemiological, research, outbreak reports and observational studies. This protocol was registered in PROSPERO (CRD42021234754). The review will be elaborated according to the PRISMA-P checklist as guidance<sup>25 26</sup> (online supplemental material 1).

### Eligibility criteria

This systematic review will evaluate published articles of observational studies, cohort, case-control, cross-sectional and ecological studies. Also, it will include case reports, surveillance and outbreak reports, report case where leptospirosis infection will be presented as infection with an infectious bacterial, viral or parasite disease. Randomised control trial study designs will not be included in this review because the coinfections occur naturally and cannot be controlled. We will consider revision or meta-analyses, as there are no systematic reviews of coinfection in leptospirosis.

### Population

This review will include all populations with a suspected or confirmed leptospirosis case and any infectious diseases detected simultaneously. Children and adults' cases will be included. We will consider all the risk factors, sites of occurrence and association with infection sources. Also, if the treatment was or was not administered and if the patient died or had another clinical outcome. All the information could be considered if the infection of leptospirosis has been associated with coinfection with one or more infectious aetiologies.

### Coinfections consideration

Coinfection will be defined as a simultaneous infection of a host by multiple pathogen species. In this review, we will include coinfections reported with any micro-organism that causes a bacterial, viral or parasitic disease.

### Types of outcome measures

The outcome of this review is to quantify the coinfections with leptospirosis and its clinical course, affectation

due to complication or death, as well as treatment used. We will be taking leptospirosis cases using the definition provided by the WHO as well as leptospirosis cases confirmed by clinical diagnosis and laboratory tests.

### Information sources

In the systematic revision, we will conduct a search using databases including LILACS, ProQuest, PubMed and Scopus to identify potential studies (online supplemental material 2). In the research, published articles from 1950 to May 2022 will be included. Grey literature will also be searched in all relevant resources listed by Paez.<sup>27</sup> Also, we will contact the authors of the studies in grey literature with relevant data to be included in the review. The references of the studies will be revised to identify possible eligible studies.

This review will include studies without language restrictions. In the cases of the articles from a language different from Spanish and English, we will translate them into English languages for inclusion in this review.

### Search strategy

The search strategy was developed in collaboration with all the authors (online supplemental material 2). The MeSH terms and DeCS-Health Science Descriptors and their synonyms (keywords) were verified in each database. The search terms were combined by using the Boolean operators 'AND' and 'OR.'

### Selection of studies

The initial screening of abstracts and titles will be performed by four reviewers independently and using the Rayyan free available (<https://rayyan.qcri.org/welcome>).<sup>28</sup> The articles will be classified for inclusion, exclusion or doubt for selection concordance among the researchers as this app allows to complete a consensus with the researchers. The decision of inclusion will be based on the eligibility of this review by reading the title and the abstract. In the case, that the title or the abstract is clear for the selection, a full-text article read will be done. Finally, the four reviewers will discuss the eligibility for all the articles. Disagreements will be resolved by a fourth investigator. From the selected studies, data will be extracted into an Excel database a cross-checked for inclusion criteria from various selected databases.

### Data extraction

The data will be selected from the articles, to be extracted into an Excel database. Then, one researcher will extract the study characteristics including title, author, region, year, source and coinfection micro-organisms. Once the information is extracted, two authors will review the type of study or design, method of screening and confirmation, sample size, mean age or age range and gender. Also, the clinical, laboratory and chemical results (types of laboratory testing, laboratory findings, serological information), treatment administered, outcomes as a description of leptospirosis for diagnosis outcome and clinical information. From the patients or participants included

in the studies, the extracted information will include age, gender, symptoms (fever, rash, jaundice, myalgia, headache, vomiting), resolution of the study if the patient died or lived. Types of exposures or risk factors, comparison, clinical information, types of laboratory testing, laboratory test and serological information. The inclusion or exclusion of the article will be summarised in a PRISMA flow diagram.

### Quality assessment

The articles will be reviewed independently by three researchers to avoid bias. We will also include the quality assessment criteria checklist by the leptospirosis Burden Epidemiology Research Group from the WHO.<sup>29</sup> Three authors will independently review the list of biases for each study according to the criteria incorporated into the Checklist for quality evaluation of disease sequelae studies (with the high, medium and low). Also, we will consider the Grading of Recommendations, Assessment, Development and Evaluation elements consisting of study limitations, reliability of effect, imprecision and publication bias.

### Data analysis

The data from the article will be extracted into Excel to have the variables for conducting a descriptive data analysis using the free programme R Studio. The variables be included : (1) proportion or counts of cases and (2) frequencies of the used test for the confirmation. The occurrence distribution will be spatially mapped. The disease with the infection will be analysed as a dichotomous variable presented in OR, risk ratio (RR) or prevalence OR with a 95% CI. Including, some complications of the diseases and the coinfection presence, types of infection and death, and treatment administered in leptospirosis, and the coinfection. We will analyse the ORs and RRs using the random-effects model for types of the coinfection as risk factors of complication stratified by sex and occurrence place (tropical, subtropical, endemic area or countries with low cases of leptospirosis). Publication bias will be assessed by Bregg's rank correlation and Egger's weighted regression methods, and funnel plots will be generated in R free V.4.0.5.

### Ethics and dissemination

This study will be based on previously published data. Therefore, the ethical review was not considered. The findings and results will be shared in conferences and peer-reviewed journals in the field of infectious diseases.

### Patient and public involvement statement

Patients will be not involved in this study. The systematic review will be made by using the criterium for the inclusion of the studies.

### Author affiliations

<sup>1</sup>Grupo de Salud Ambiental y Laboral, Instituto Nacional de Salud, Bogotá, Colombia

<sup>2</sup>Subdirección de Estudios Clínicos y Epidemiología clínica, Fundacion Santa Fe de Bogota, Bogota, Colombia



<sup>3</sup>Multidisciplinary Initiative for Collaborative Research in Bacterial Resistance (MICROB-R), Santiago, RM, Chile

<sup>4</sup>Grupo de Microbiología, Instituto Nacional de Salud, Bogotá, Colombia

<sup>5</sup>Morgridge Institute for Research, Madison, WI, 53706, United States of America, Madison, Wisconsin, USA

<sup>6</sup>Department of Medical Microbiology and Immunology, University of Wisconsin, Madison, Wisconsin, USA

<sup>7</sup>Escuela de Medicina Veterinaria, Facultad de Agronomía e Ingeniería Forestal, Facultad de Ciencias Biológicas y Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

<sup>8</sup>Departamento de Medicina interna, Fundación Santa Fe de Bogotá, Bogotá, Colombia

<sup>9</sup>Departamento de Medicina crítica y cuidado intensivo, Fundación Santa Fe de Bogotá, Bogotá, Colombia

<sup>10</sup>Facultad de Medicina, Universidad El Bosque, Bogota, Colombia

**Twitter** Nicolhole Atero @Naatero3

**Contributors** Conceiving the protocol: ELP. Designing the protocol: ELP, ERS and GMGL. Coordinating the protocol: ELP, GMGL, NA, SB, AB and ERS. Designing search strategies: ELP, SB, NA and AB.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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#### ORCID iD

Eliana L Parra Barrera <http://orcid.org/0000-0002-2745-7997>

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