BMJ Open

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

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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

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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.

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.

INTRODUCTION

Leptospirosis is a zoonotic disease caused by spirochaete bacteria *Leptospira* and constitutes a neglected tropical disease with worldwide distributions.[1 2] In 2015, it was estimated that 1,03 million leptospirosis cases occur annually with a global burden of 58 900 deaths[3] and 2.90 million disability-adjusted life-years annually, affecting especially the tropical and endemic areas.[3 4] 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.[1 5–10]

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.[4 9 11–13] Human leptospirosis infection usually is initiated as acute undifferentiated fever.[13 14] Then the infection presents a wide variety of symptoms (eg, headaches, jaundice and complications such as kidney and liver failure)[9] that also occur in other infectious diseases.[15] As leptospirosis is more frequent in tropical countries, it could be present simultaneously with other febrile syndromes induced by malaria, dengue,[16 17] Zika,[18] chikungunya and hantavirus, among others.[7 19] Therefore, early diagnosis is

challenging as the disease presents non-specific symptoms and is indistinguishable from other tropical acute febrile illnesses.[15 20]

There is epidemiological synergy between leptospirosis outbreaks and other aetiologies such as viral infections including chikungunya, dengue[16 21] and Zika,[18] parasitic infections such as malaria or babesia, and bacterial infections such as rickettsiosis,[7] borreliosis and melioidosis,[22] 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,[23] 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.[3 4 11] Also, leptospirosis is an undifferentiated febrile infection like other febrile diseases.[2 14 24] In the last years, several reports, studies, outbreaks and research have reported coinfection with febrile diseases.[7 16–19 21] 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 coinfected 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.[25] 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[25 26] (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.[27] 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).[28] 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.[29] 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.

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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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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Answer	Page
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Yes	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No	No Applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes	2 and 16
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	15 and 16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	No	No Applicable
Support:				
Sources	5a	Indicate sources of financial or other support for the review	No	No Applicable
Sponsor	5b	Provide name for the review funder and/or sponsor	No	No Applicable
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	No	No Applicable
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	2 to 7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	8 to 9
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes	9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes	11 and supplementary 2
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such	Yes	11 and supplementary 2

		that it could be repeated		
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	12 to 14
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility, and inclusion in meta-analysis)	Yes	12 to 14
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes	12 to 14
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes	
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	No Applicable
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)		
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	No	No Applicable
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	No	No Applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	No	No Applicable
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	No	No Applicable

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review andmeta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary Table. Search terms selected according by each database

Name	Search Strategies
LILACS	(tw:((tw:("Leptospirosis")) OR (tw:("Leptospira ")) OR (tw:("Weil syndrome")) OR (tw:("Weil´s syndrome")) OR (tw:("leptospirosis infection")) OR (tw:("human leptospirosis")) OR (tw:("Leptospirosis in humans")) OR (tw:("jaundice fever")) OR (tw:("leptosira interrogans"))) AND (tw:(co-infection OR coinfection OR co-occurrence OR secondary infection OR dengue OR virus OR hantavirus OR febrile illness OR malaria OR borreliosis OR zika)) AND (tw:(("misdiagnosis") OR ("confirmation diagnosis") OR ("delayed disease") OR ("no confirmed") OR "endemic" OR "melioidosis" OR "rickettsiosis")))
PROQUEST	((TI("Leptospirosis" OR "Leptospira" OR "Leptospira interrogans" OR "pathogenic leptospirosis") AND ("co-infection*" OR "co-occurrence" OR "coinfection" OR "Weil syndrome" OR "Weil´s syndrome" OR "leptospirosis infection" OR "human leptospirosis" OR "Leptospira interrogans") AND ("malaria" OR "dengue" OR "zika" OR "melioidosis" OR "brucellosis" OR "rickettsiosis" OR "rickettsia" OR "hantavirus" OR "virus" OR "borreliosis")) OR AB(("misdiagnosis" OR "confirmation" OR "confirmation diagnosis" OR "delayed diseases") AND ("diagnosis*" OR "disease" OR "ELISA" OR "MAT" OR "agglutination" OR "no confirmed" OR "pathogens" OR "scales") AND ("tropic" OR "endemic" OR "emerging diseases" OR "febrile illness" OR "fever" OR "jaundice" OR "myalgia" OR "re-test" OR "lepto" OR "diagnosis")))
PUBMED	(("Leptospirosis" [Title/Abstract] OR "Leptospira" [MeSH Terms] OR "lepto" [Title/Abstract] OR "Gram-negative spirochete"[MeSH Terms] OR "leptos"[Title/Abstract] OR "Leptospira interrogans" [MeSH Terms] OR " Pathogenic Leptospira" [Title/Abstract] OR "Weil syndrome" [MeSH Terms] OR "pulmonary hemorrhage" [Title/Abstract] OR "acute respiratory distress syndrome" [Title/Abstract] OR "IgM Leptospira antibodies" [Title/Abstract] OR "Weil's syndrome" [Title/Abstract] OR "leptospiral infection"[Title/Abstract] OR "Leptospirosis infection" [MeSH Terms] OR "Leptospira spp" [Title/Abstract] OR "jaundiced fever" [MeSH Terms]) AND ("Coinfection" [Title/Abstract] OR "co-infection" [MeSH Terms] OR "infectious" [Title/Abstract] OR "febrile illness"[Title/Abstract] OR "Rickettsia" [Title/Abstract] OR "Brucellosis" [Title/Abstract] OR "Borreliosis" [MeSH Terms] OR "arthropod-borne viruses" [Title/Abstract] OR "chikungunya" [Title/Abstract] OR "Babesia" [Title/Abstract] OR "Hantavirus" [Title/Abstract] OR "virus" [MeSH Terms] OR "parasite diseases" [Title/Abstract] OR "virus diseases" [Title/Abstract])) AND ("Leptospirosis"[Title/Abstract] OR "secondary infection"[MeSH Term] OR "" [Title/Abstract] OR "Melioidosis" [MeSH Term] OR "Co-occurrence" [Title/Abstract] OR "misdiagnosis" [Title/Abstract] OR "delayed diagnosis" [MeSH Term] OR "pathogens" [Title/Abstract])
SCOPUS	**(**TITLE-ABS ("Leptospirosis" OR "Leptospira" OR "Leptospira interrogans" OR "Weil syndrome" OR " Pathogenic Leptospira" OR "Leptospira interrogans" OR "acute respiratory distress syndrome" OR "Weil's syndrome" OR "lepto" OR "IgM Leptospira antibodies" OR "leptospiral infection")) AND (TITLE-ABS ("Coinfection" OR "co-infection" OR "infectious" OR "Febrile illness" OR "Rickettsia" OR "Brucellosis" OR "arthropod-borne viruses" OR "secondary infection" OR "Co-occurrence" OR "dengue" OR "Melioidosis")) AND (TITLE-ABS ("delayed diagnosis" OR "misdiagnosis" OR "delayed diagnosis" OR "pathogens" OR "parasite disease" OR "Borreliosis" OR "virus" OR "chikungunya" OR "Hantavirus"))
Grey literature	Google Scholar, official web pages of ministries of health, health entities, national health institutes, case reports in non-indexed medical journals. Using key words as: leptospirosis, Leptospira, Leptospira interrogans, febrile syndrome, coinfection, co-infection, co-occurrence.